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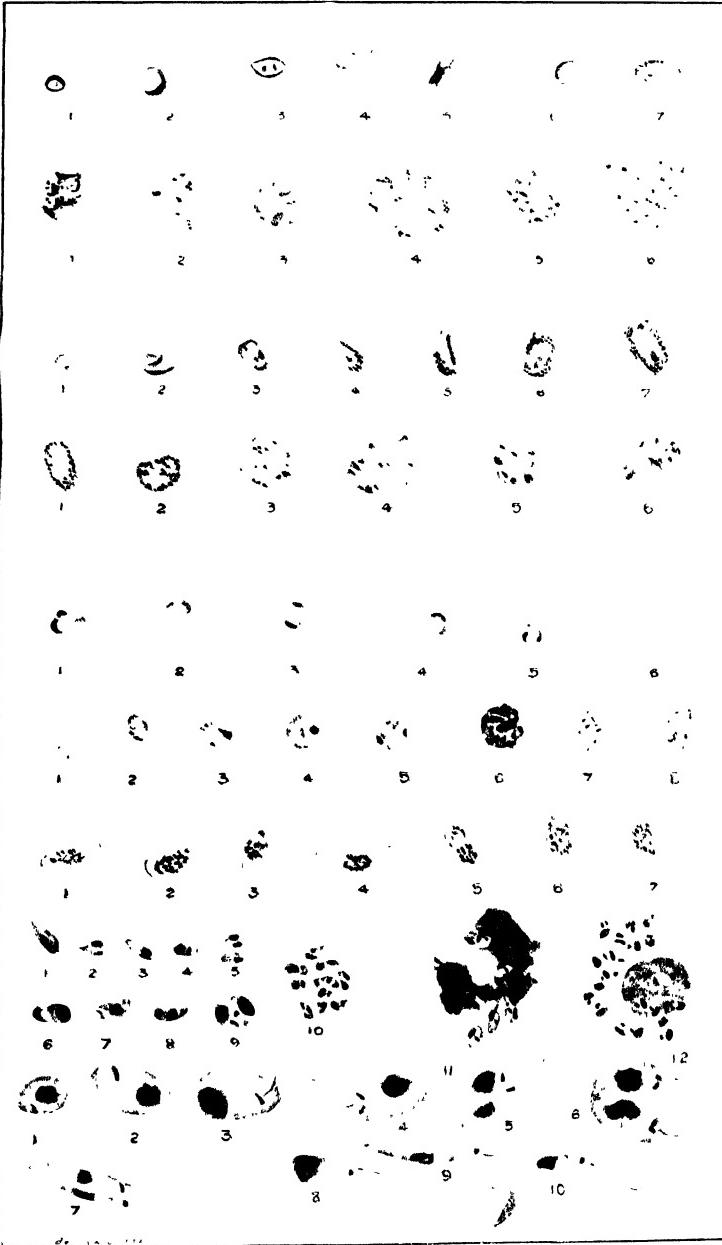
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FEVERS IN THE TROPICS

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FEVERS IN THE TROPICS

BY

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THIRD EDITION

"It is remarkable how entirely the most distinguished physicians of all ages who have treated of this subject (fever) coincide in the feeling that with regard to this important class of diseases it is impossible, in the short life allotted to the most aged, to do anything more than to add a little knowledge to the common stock."

—DR. SOUTHWOOD SMITH.

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1919

MY BROTHER OFFICERS OF THE INDIAN MEDICAL SERVICE

TO WHOM I AM INDEBTED FOR SO MANY OPPORTUNITIES OF RESEARCH

THIS WORK IS RESPECTFULLY DEDICATED

PREFACE TO THIRD EDITION

TEN years of very active advance in tropical medicine have passed since the first edition of this work appeared, and eight since the partial revision for the second edition. Very extensive alterations and additions have therefore become necessary to bring it up to date. Unfortunately this heavy task had to be undertaken in the midst of active duty in the tropics, and it has only been rendered possible by the literary work of the author on tropical diseases for the *Medical Annual* during the last seven years, and by the immense help he has derived from the two reviews of recent advances in tropical medicine of the Wellcome Research Laboratories, Khartoum, of 1908 and 1911, by Dr. Balfour and Captain Archibald, the *Yellow Fever Bureau Bulletin* of the Liverpool School of Tropical Medicine and the *Kala-azar and Tropical Diseases Bulletins* published by the Royal Society under the editorship of Dr. A. G. Bagshawe and Dr. Wenyon. He is glad of this opportunity of acknowledging the great boon these publications are to himself and all workers in the tropics.

The following are the main alterations in the present edition. The section on kala-azar has been largely rewritten, and much of the epidemiological portion and of the details of the author's own researches have been omitted to make room for new work and reduce it to due proportion with the rest of the book. Nearly every section has been extensively revised, and most of them rearranged so as to give the history, geographical distribution, etiology and prophylaxis before the clinical section in the hope of making the work more readable. Especial attention has been devoted to the treatment of those diseases for which more or less specific drugs are available, including kala-azar, trypanosomiasis, malaria and amoebic hepatitis. Recent work on typhus has been included and short articles added on Oroya fever, infective jaundice and "trench fever," regarding which important advances have recently been made, in the hope that some account of them may be of use to the numerous medical officers serving with the British and Allied Armies in subtropical countries. The historical introduction and the article on epidemic dropsy,

which is now generally considered to be beriberi, have been omitted, and the section on blood examination has been reduced and distributed under appropriate sections, as with the improved teaching of tropical medicine a separate section no longer appears to be necessary. The section on liver abscess has also been omitted as it has appeared in the author's book on dysenteries, to which it more properly belongs.

The author trusts that allowance will be made for the many remaining imperfections on account of the difficult circumstances attending the revision.

He is greatly indebted to Dr. R. M. Wilson for reading the proofs, and to the Publishers falling in with his suggestion to make the volume a lighter and more handy one.

PREFACE

I HAVE attempted in this work to write an original account of fevers in the tropics, mainly based on the notes and charts of some two thousand cases in which I have personally examined the blood by modern diagnostic methods. It includes the Milroy lectures on Kala-azar, with the clinical parts greatly amplified and a description of its early stages which have hitherto not been recognized. The fever which constitutes the pre-suppurative stage of amoebic abscess of the liver, and its rapid cure, is also described for the first time ; this method has, in the Calcutta European Hospital, led to a great reduction in the number of cases of abscess of the liver. Sections on unclassified fevers of the tropics include descriptions of "seven-day fever" first differentiated from malaria by the author, also the three-day fevers recently recognized in India. Accounts of sleeping sickness and yellow fever have been included, at the suggestion of Professor Osler, based on the recent extensive investigations on those subjects. The technique and the diagnostic value of microscopical examinations of the blood in fevers is described, as far as it can be carried out in a hospital without a bacteriological laboratory.

All the illustrations are original, and include four-hourly temperature charts. The writer has been led by his researches to conclude that a large proportion of fevers in the tropics can be diagnosed within two or three days by purely clinical methods. It will thus become possible in the remaining doubtful cases for a microscopical examination of the blood to be made as a matter of routine, and a clear idea to be got of all fever cases, whereas under ordinary conditions of work in the tropics time does not permit of the use of the microscope in every case. Should this hope be in any degree fulfilled, the work should be of value to medical men in the tropics, both as an aid in the early diagnosis of these very common diseases and to those engaged on researches on the still undifferentiated fevers of hot climates.

References to the most important literature have been given at the end of each section, arranged chronologically, so as to illustrate their history ; the evolution of our

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present knowledge and nomenclature has been traced in the introductory section, the practically important subdivision into long, and short fevers has been adopted, as a strictly scientific one is not yet possible.

I desire gratefully to acknowledge the kindly interest and advice given me by Professor Osler.

I am very much indebted to Mr. J. Keogh Murphy, F.R.C.S., for very kindly revising the proofs and for many valuable suggestions. My acknowledgements are also due to Dr. C. R. Schofield and Miss Kelley for many of the illustrations and work of the charts.

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A. Fevers of Long Duration

I. KALA-AZAR (INDIAN AND MEDITERRANEAN OR INFANTILE FORMS)

HISTORY AND EPIDEMIOLOGY

The Assam Epidemic.—Kala-azar first attracted public attention in 1882 in the Garo Hills of Assam (see map, page 2), where it was causing a high mortality, and was called "black fever" by the Garos. Notes of 120 cases were then recorded as "malarial cachexia" by the Civil Medical Officer, Mr. McNaught. On examining the district records in 1897 I found that the increased mortality due to the disease, as shown by falling off in the Government revenue, dated from 1875, and by 1881 numerous villages at the foot of the hills had been wiped out. Moreover, the disease appeared about 1875 at two places fifty miles apart, where the two main ferries across the Brahmaputra River communicate with the Rungpore district to the west, while between 1871 and 1876 a terrible outbreak of fever took place in the Rungpore and adjacent Dinajpore districts associated with an unprecedented series of five out of six consecutive years of deficient rainfall, which always causes an increase of fever in that area. Further evidence that this Rungpore outbreak is intimately connected with the Assam epidemic is found in the fact that kala-azar was also later found to be very prevalent in the north-west portion of the Dinajpore district and adjacent parts of the Purnea districts, where a high mortality was caused by it under the name of kala-dukh, while the still more westerly Bihar districts are at the present day important endemic areas of the disease. A careful survey of the records of the great Burdwan Epidemic Fever of 1854–73, which devastated much of Western Bengal, convinced me that it was also kala-azar, but other workers dissent from this view, which it is impossible to prove after this lapse of time, although my Calcutta records and Muir's work at Kalna in the Burdwan district show that the disease is still endemic to a great extent in that division of Bengal.

However that may be, the most striking feature of the Assam epidemic was the way in which it spread steadily year by year in an easterly direction up the Brahmaputra valley, following the roads and lines of communication at the rate of about ten miles a year, and passing on as a wave of greatly increased mortality in each infected district of some ten years' duration, and then declining, but leaving sporadic cases of the disease behind it, which still persist in the Garo Hills over forty years later. In the map the large figures show the period of years during which the mortality was excessive in each district, and the smaller ones the dates at which the disease attacked different places,

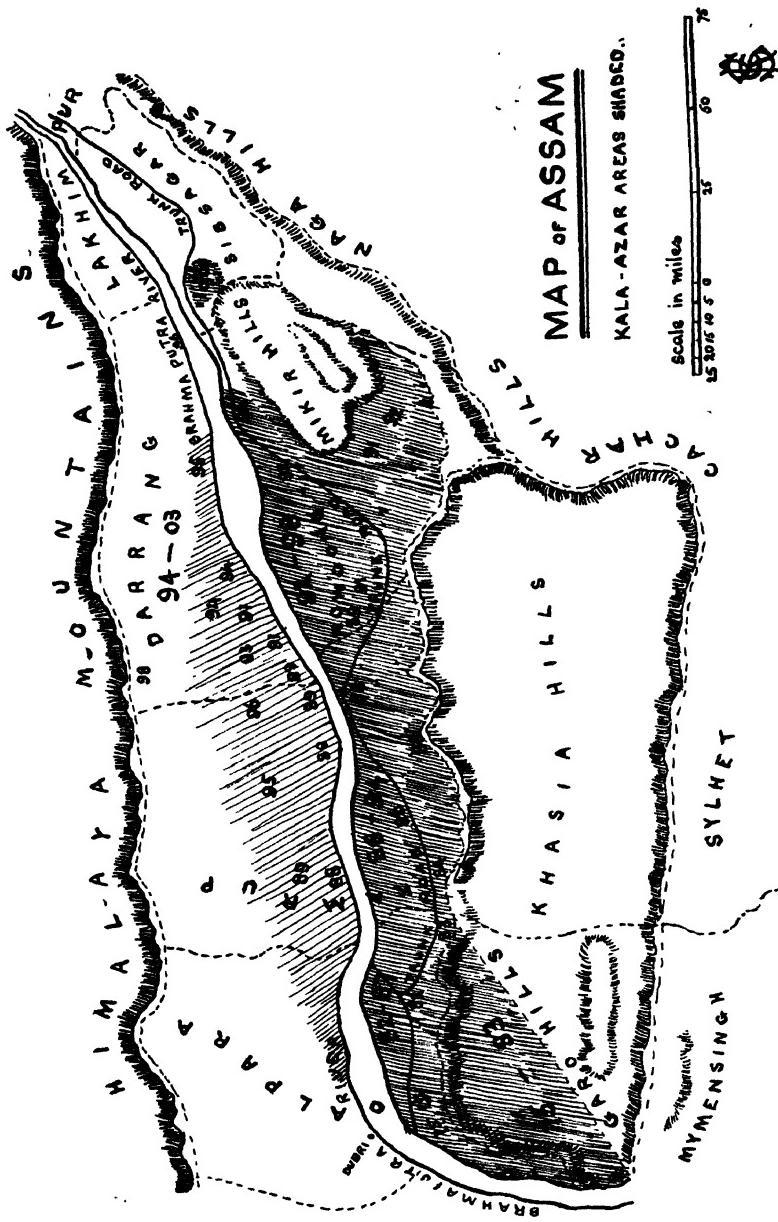


DIAGRAM I.—Map of Assam illustrating spread of Kala-azar.

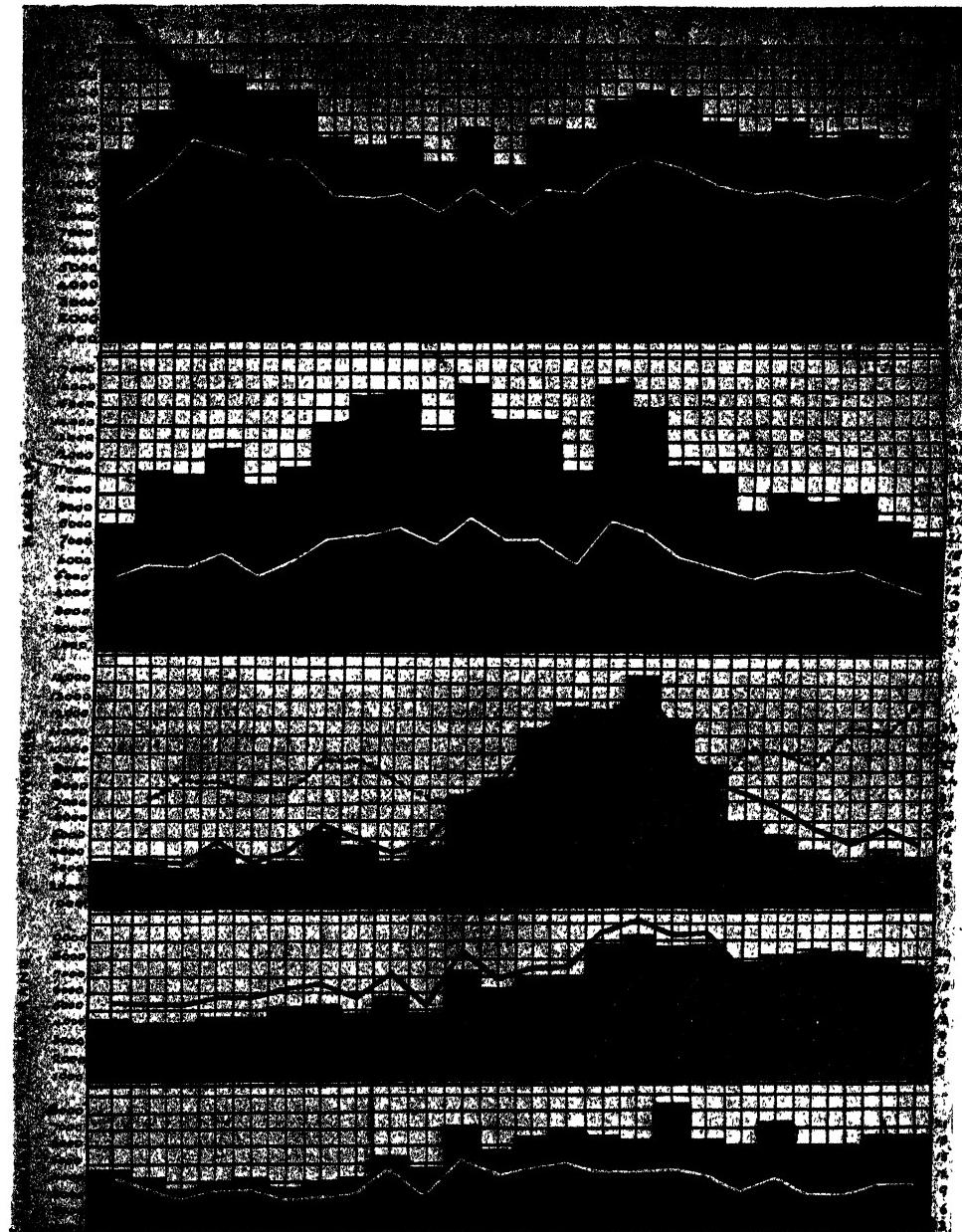


DIAGRAM II.—Yearly fever district death-rate.

which makes it unnecessary to describe the spread in further detail. Diagram II. gives the yearly fever death-rates for each district from 1882 to 1905, and shows the waves of mortality, that of the Nowgong district being the most striking as the whole of it was severely affected, while in the case of Goalpara and Kamrup districts only the smaller portions south of the Brahmaputra River suffered severely. To the east of the Nowgong district lie the sparsely inhabited Mikir Hills, and to their south the almost uninhabited Namba Forest, while the main line of communication with the Sibsagar district to the north-west passes along the narrow track between the Mikir Hills and the Brahmaputra River, which is also thinly peopled. Recognizing the great importance of taking advantage of this natural barrier as an aid in checking the farther easterly progress of the epidemic, in my report of 1897 I advised that precautions should be taken to prevent infected persons going east from the Nowgong district, and that if any villages became infected on the Golaghat division of the Sibsagar district they should be dealt with as advised under prophylaxis. These measures were both carried out subsequently with a considerable degree of success, and with the expected decline in the Nowgong district during the first decade of the present century the total recorded death-rate from kala-azar (including cases of the sporadic disease in the very densely populated Sylhet district, to the south of the Khasia Hills, which the epidemic did not affect), fell steadily from a total of 6319 in 1902 to 1703 in 1909. Unfortunately there has since been a slight increase in the Nowgong district, and a more serious appearance of the disease in the central portions of the Sibsagar district, although it is to be hoped in a less epidemic form than formerly, while with our present effective preventative and curative measures the disease will be much easier to deal with.

The appalling mortality caused by the Assam epidemic can be gathered from a study of the Diagram III. on page 5, in which are shown the census figures from 1872 to 1901 in three decades, in the first of which the Garo Hills suffered most, in the second the Garo Hills showed an increase of 11.2 per cent, a good recovery, while the Goalpara and Kamrup districts recorded a decrease in the population of 18.1 and 11.6 per cent against increases in unaffected more easterly districts of from 10.4 to 18.8 per cent; while in the third decade the Nowgong district showed the terrible reduction of no less than 31.5 per cent in its indigenous population in ten years, against an increase in the easterly Sibsagar and Lakimpur districts of 8.6 and 16.3 per cent. Happily the census figures of 1911 show an increase of 14.76 per cent in the population of the sorely afflicted Nowgong district, which is no doubt continuing during the present decade. The remarkable decline in the mortality from fevers in Nowgong will be evident from the fact that at the height of the epidemic in 1897 the figure reached 14,500, the very great majority of which were certainly due to kala-azar, while in 1905 only 379 deaths were returned as due to this disease. The sporadic affection, however, remains and is likely to continue to do so, as in all other infected districts. The devastation caused by the epidemic is shown by the extent to which land fell out of cultivation, and also became quite unsaleable. Thus in the Mangaldai district Mr. (now Sir Edward) Gait supplied me with figures showing that in the Mangaldai district one-fourth of the cultivated land in the affected parts was abandoned within five years, while in Nowgong one-fifth of the land had fallen out of cultivation within a similar period up to 1895 before the height of the outbreak had

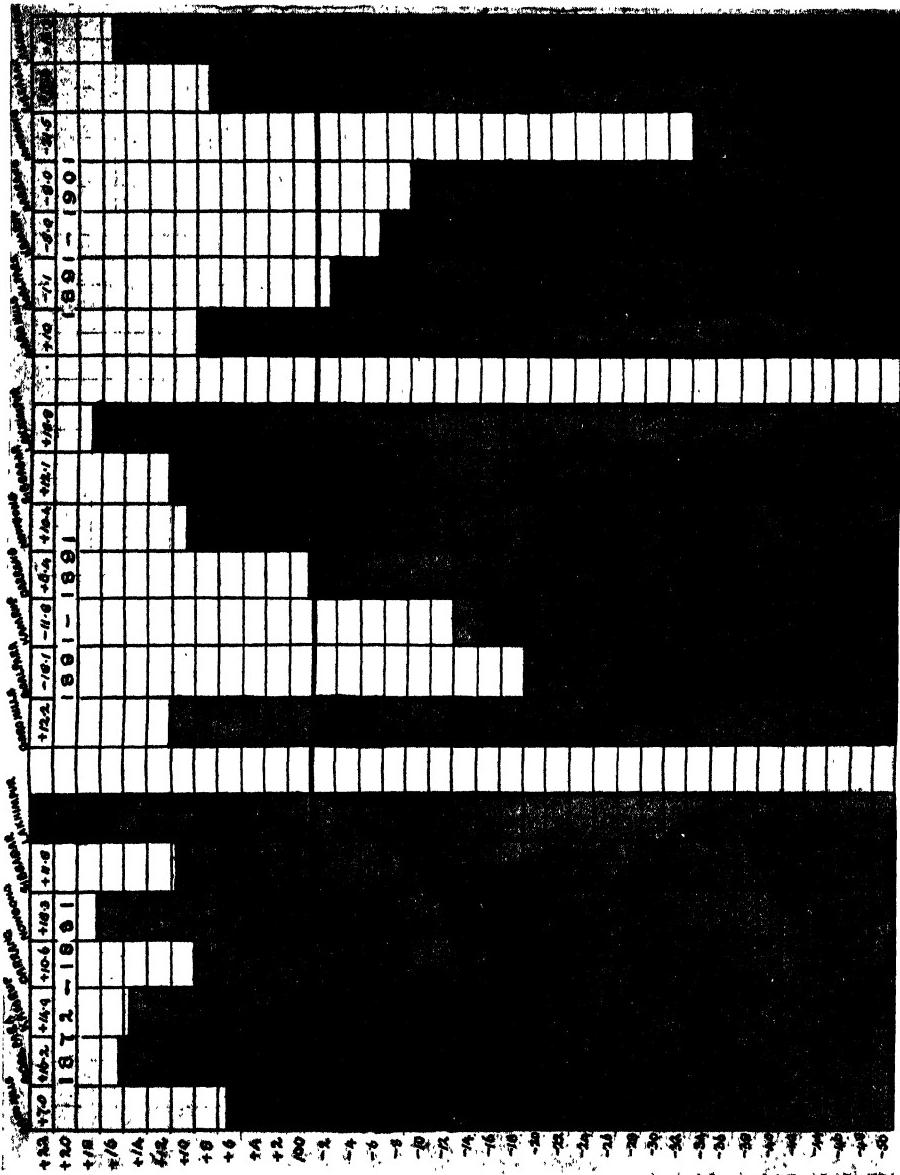


DIAGRAM III.—Census figures illustrating the variations of the population of Assam districts during the three epidemic Kali-azar decades.

been even reached in that district, so the ultimate figure was probably at least twice as high.

Such a disaster naturally led, even in those early days when India possessed no whole-time pathologist, to some effort being made to investigate the mysterious spreading disease, and in 1889 G. M. Giles was sent to Assam to inquire into kala-azar and also ancylostomiasis, which had recently been discovered in both Ceylon and the Nowgong district of Assam. He found ancylostoma ova in the stools of a majority of kala-azar cases, while it was not shown until a little later by Dobson that over 80 per cent of the imported coolies, who had passed two medical examinations, harboured this worm, so Giles concluded that "whatever kala-azar might be elsewhere, the disease so called in Gauhati (where he worked) was undoubtedly ancylostomiasis," and he further stated that enlarged spleen was so common in healthy people in Assam that "it is obviously absurd to attach any pathognomonic importance to the symptom in connexion with the etiology of kala-azar." This theory was not accepted by medical men with any knowledge of kala-azar in Assam, and as Nowgong became badly infected in 1896 it was decided to send a junior medical officer to reinvestigate the disease, and I was fortunate enough to be selected for the work, and as the result of a careful clinical, pathological, and epidemiological study of the disease during a year in Assam I erroneously concluded that it was a spreading epidemic malaria. It was not known until some years later that in highly malarious places a very large percentage of apparently healthy population may be harbouring the malarial parasites in their blood, while nine years later I found the malarial endemic index at the height of the malarial season to be over 80 per cent in the area in which I had worked, and, just as Giles attributed the disease to complicating ancylostoma, I did so to malaria. As a matter of fact I only reluctantly came to this conclusion and visited Sylhet to the south of the Khasia Hills, where kala-azar was then unknown, in order to study "malarial cachexia," which was prevalent there, to compare it with the Assam epidemic kala-azar, but I could find no difference whatever between them by the most careful clinical and blood examinations, except that the Sylhet cases were much more chronic than the Assam ones, so concluded that the Assam disease was but an epidemic manifestation of the chronic malarial cachexia seen in Sylhet. I also obtained strong evidence that the disease was a communicable one, and that the infection was essentially a house or at least a site one, on which I based recommendations for prophylaxis against the disease, which subsequently enabled its spread to be largely controlled and serious outbreaks on a number of tea-gardens to be stamped out. In 1899 Sir Ronald Ross also briefly studied kala-azar in Assam, and after a careful discussion concluded: "I think then, with Rogers, that kala-azar is malarial fever." In 1902 Bentley declared the disease to be an epidemic Malta fever on the strength of some erroneous serum tests made at Kasauli. It was not until in 1903 Leishman and Donovan reported the independent discovery of the parasite of kala-azar that the mystery was cleared up, and the so-called malarial cachexia of Bengal and Sylhet, which I had found identical with the Assam epidemic, was then found to be sporadic kala-azar, and the recognition of the Mediterranean form of the disease soon followed.

Geographical Distribution.—With the exception of a recent outbreak of epidemic

kala-azar in the Sibsagar district of Assam, the disease in India is now of the sporadic type. The essential difference is that before the epidemic beginning in the Garo Hills there is good reason to believe that the Brahmaputra valley was free from the disease, so that it found a virgin soil in which to flourish; just as sleeping sickness did when carried to Uganda from West Africa. In Assam only parts of the Lakhimpur and Sibsagar districts of the valley remain uninfected, and the disease is increasing in these. The parts previously attacked by the epidemic now show sporadic cases, as shown by McCombie Young, who in a special investigation during 1912-13 found the sporadic disease had almost exactly the same distribution as I described in 1897, except for some slight spread eastwards. In Bengal an analysis of 66 recent endemic cases in my ward in Calcutta showed that the largest number had contracted the disease in Calcutta (24), while the Burdwan (11), Presidency (12), and Rajshahi (6) divisions, in which the Burdwan epidemic fever and kala-dukh had formerly been epidemic, gave most rural infections. I have long suspected that resort to prostitutes is a likely source of infection through the bites of bed bugs, and the number of Calcutta infections lends some support to that suspicion. Bihar (6) gave the next largest numbers of cases, although at a greater distance from Calcutta, and especially the northern districts are much affected, many cases being seen in the large Patna hospital. Only one of my cases came from Orissa, and none from Chota Nagpur, where the disease is probably comparatively rare. In the United Provinces the eastern districts bordering on Bihar are certainly infected, while in 1914 I found a case in the Lucknow hospital from an adjacent district, and others have been met with since. Cases have been reported as far west as Dehra Dun, but may have been imported. The Punjab and Bombay Provinces only record imported cases. Madras has a serious focus of infection in the poorer quarter, Blacktown, while isolated cases have been recorded as far south as Madura and Trichinopoly. Burma and the Malay States have had imported cases.

Asia is also infected far beyond India. Thus the parasites have been identified from the organs of patients who have returned from China by several observers, the first apparently by Marchand and by Bassett-Smith in several sailors, and in 1910 Aspland showed the disease to be fairly common in North China, usually in children from two to ten years old. In 1911 Cochran recorded the results of an inquiry he had made in China by means of letters, and Jeffreys and Maxwell report on it also in their book on *Diseases of China*, from which sources it appears to be endemic in the area to the north of the Yangtse River between the coast and a line joining Pekin and Hankow, while a case has also been reported on the Upper Yangtse at Ichang. Russian Turkestan is also an endemic area, Zakimoff having reported cases from Andijan, Askabad, Tashkent and Termese, and one from as far north as Tobolsk. The Caucasus also reports a few cases.

Mediterranean or Infantile Kala-azar.—The announcement of the discovery of the Leishman-Donovan parasite of kala-azar was soon followed by the recognition of a form of the disease affecting mostly young children, and prevalent in the countries bordering on the Mediterranean. In 1904 Cathoire noticed in films from a child's spleen from Tunis certain bodies which Laveran recognized as Leishman's bodies, and Nicolle and

Cassuto punctured a number of enlarged spleens and found the same parasite in a child with symptoms of kala-azar in 1907. In the meanwhile Pianese also found them in 1905, and further cases were soon met with from a number of Mediterranean countries : by Archer in Crete ; Gabbi in Sicily ; Critien at Malta ; Gabbi in Spezzia in a disease known locally as Ponos, and Christomanos independently at Paros, both in Greece. Further work established as endemic areas Algeria, Tunis, Tripoli, Libya, Egypt, the Sudan (Marshall and Archibald), Asia Minor, Greece, Crete, including the Ionian and many other islands, Corfu, numerous places in Sicily and South Italy up to Rome, Malta, the south and eastern coasts of Spain, and the west coast of Portugal : in short, the whole of the Mediterranean basin, and somewhat beyond it.

The great incidence of the disease on young children, and the fact that dogs are infected with a similar parasite, together with some supposed slight differences in symptomatology led to infantile kala-azar being considered by some to be distinct from the Indian variety, but as more cases were described the clinical differences disappeared one by one, and nearly all authorities now consider that there are not sufficient grounds for separating them. The few remaining differences regarding animal infection and probable modes of transmission will be considered under etiology, but the symptoms do not require any separate description.

ETIOLOGY

Kala-azar as a Communicable Disease.—In 1897, when I commenced my investigation in Assam, the general medical opinion regarding the epidemic of kala-azar was that the disease was a virulent form of malaria, and therefore it could not be infectious, those being the pre-Rossian days before the mosquito theory of malaria was seriously regarded, much less proved. Careful inquiries made during a 150-mile tramp from village to village, in a district where the disease was actively spreading, furnished me with convincing evidence that the infection was carried from one place to another by infected persons, and that the infection was essentially a house one (see my 1897 Report on Kala-azar and my Milroy Lectures of 1907). I also obtained evidence on tea-gardens that newly imported unaffected coolies could safely be placed in new lines only two hundred yards or so from old infected ones, and on these facts I based the prophylactic measures which proved successful in ridding tea-estates of this terrible plague, and that, too, before the true nature of kala-azar had been discovered. The communicability of the disease was thus clear, although its causation remained to be discovered.

Discovery of the Parasite of Kala-azar.—The parasite of kala-azar was independently found by more than one observer, but to W. B. Leishman, R.A.M.C., belongs the credit of having had the courage to first describe it, two and a half years after he had seen it, as probably a degenerate stage of a human trypanosome, not very long after that organism had been found in a fever in Africa by the late Dr. Dutton, while Rose Bradford and Plimmer had previously described a form of the *Trypanosoma brucei* similar to the bodies Leishman found. As soon as Leishman's paper reached India, C. Donovan, I.M.S., recorded that he had independently observed the same bodies in the spleens of patients dying of prolonged fever in Madras one month before Leishman's note was published,

and as he was also able to find them in fresh splenic blood obtained by puncture of the organ during life, he was able to disprove Leishman's suggestion that they were degenerate trypanosomes, for the flagellate form of the organism has never been found in the human system. Laveran and Mesnil, after examining specimens sent by Donovan, concluded that the organism was a piroplasma, while J. H. Wright of Boston, at the end of 1903, described similar bodies to those of Leishman and Donovan in a form of chronic ulceration met with in the Punjab known as Delhi boil, in which D. D. Cunningham had, as early as 1885, described the aggregations of these peculiar bodies. As kala-azar is unknown in the Punjab there is good reason to believe that the parasite of Delhi boil is quite a distinct species from that of the Assam fever.

The papers just referred to appeared while I was on leave in England, and I quickly realized, as was also suggested by Donovan, Ross, and others, that if many of the cases previously known as "malarial cachexia" were really caused by the new parasites, then kala-azar of Assam must be also produced by it, for I had shown in my report that the Assam outbreak was but an epidemic form of the so-called "malarial cachexia." On returning to India at the end of 1903 I obtained some slides of splenic blood of kala-azar patients from my friend, Dr. Dodds Price, and readily found the new parasites in them, as well as in several cases of chronic spleen fever in the Dinajpur district, which were evidently the sporadic form of the same disease. At about the same time Dr. Bentley independently found the same parasites in kala-azar cases, and published his observations shortly before my own appeared in print. Other cases in Dinajpur with large spleens following chronic fever showed only malarial parasites in their spleen blood; and I found it impossible at a single examination to differentiate between the two forms clinically, although subsequently able to do so by the blood changes already described. It is not, therefore, surprising that kala-azar has been so long confounded with chronic forms of malarial fever; and the discovery of the new parasite has done more towards clearing up the fevers of Bengal and some other parts of India than anything else since Laveran's description of the parasites of malaria. "The Mediterranean form of kala-azar was soon after found to be also caused by a parasite indistinguishable from *L. donovani*." The discovery of the new parasite thus furnished the key to a problem which a century of clinical observation had been unable to unlock.

The Protozoal Parasite, *Leishmania-Donovani*.—The appearance of the parasite in the human body when stained with one of the numerous modifications of Romanosky's stain, as seen under a $\frac{1}{2}$ th oil immersion lens and No. 2 eye-piece, is shown in Line VIII. of the frontispiece, and unstained in the first line of Plate 1, opposite page 12. They are minute bodies about the size of blood platelets, but characterized by a larger oval nucleus and a smaller rod-shaped more darkly staining micronucleus. No. 11 of Line VIII. of the coloured plate shows several parasites within a polynuclear leucocyte, while No. 12 shows the minute forms within the endothelial cells of the capillaries as seen in very large numbers in smears of the spleen pulp obtained at a fresh post-mortem on kala-azar cases. When a slide is made from blood obtained during life by spleen puncture the larger separate forms are obtained owing to those endothelial cells in which the fullest development has taken place, rupturing and setting them free under the suction action of the syringe, but

groups of intermediate-sized parasites are also sometimes seen as shown in figure 10 of Line VIII. Division of these bodies takes place by the micronucleus first dividing into two followed by that of the macronucleus, and then the body splits into two, figure 9 of Line VIII. showing the condition just before division of the body. These are the only forms found in the human body, although Wenyon has recently discovered a flagellate stage in the Leishmania tropical of oriental sore in a dog within the bone marrow.

Distribution of the Parasite in the Human Body.—It soon became apparent from the observations of Manson, Low, Ross, and especially of S. R. Christophers, I.M.S. (who had been placed in special duty by the Government of India to work at the subject in Madras), that the organism may be found in practically every organ of the body in variable numbers, although it is most numerous in the spleen, bone marrow, and liver. They were also occasionally observed in the mesenteric glands, and more rarely in ulcers in the intestines, and both Manson and Christophers suggested that they might escape in the faeces, and so reach water, through which reinfection of others might take place.

Christophers' microscopical studies showed that the parasites multiplied mainly in the large endothelial or macrophagic cells of the spleen and bone marrow especially, until the invaded cells bulge into the lumen of the vessels. During the operation of spleen puncture those containing the largest parasites rupture most readily, and the organisms thus obtained are nearly all the larger capsulated ones shown in figures 1 to 10 of Line VIII. of the coloured plate in contrast with the many minute ones seen in a spleen smear made post-mortem as in figure 12 of Line VIII. of the coloured plate. A similar rupture of the distended endothelial cells must also frequently take place naturally in the body, and so allow of the entrance of the parasite into the circulating blood and its distribution to all parts of the body, a hypothesis which also explains the large number of the organisms **found** in just those organs where malarial parasites also accumulate—namely, the spleen, bone marrow, and liver, while I have also several times found them in the brain.

The parasite is also sometimes found in small numbers in the **peripheral circulation**: a matter of great importance owing to its diagnostic value. Different observers, however, differ greatly in the frequency with which this appearance was found, probably owing to variations in the severity of the infection. Thus in Madras, where the disease is fairly acute, Donovan reported having demonstrated the parasite in 93.22 per cent of all cases, examining on the average two slides on two days, prepared by compressing the finger below the pulp for half a minute to obtain more leucocytes, as they are nearly always found within the large mononuclear or polynuclears, and spreading out the blood with the smooth-ground edge of another slide in such a way that the end forms a straight line across the slide, as here the majority of both the leucocytes and parasites will be found. Patton, also working in Madras, in 84 cases found the parasites in the first slide of finger blood in 42, in the second and third in 13 and 12 respectively, in from the fourth to the sixth in 11 more, and in the remaining 6 in from the seventh to the twentieth slide; so that in some very prolonged examinations are required for this method of diagnosis. Mackie in the acute form in Assam in 245 cases diagnosed as kala-azar, but possibly including a few doubtful cases, found the parasite in the blood in 21 per cent of indigenous Assamese, and in nearly 64 per cent of tea-garden coolies. They may, however, be absent

after repeated examinations in proved cases of kala-azar. On the other hand, in the very chronic cases seen in Calcutta and Bengal districts a number of competent observers have failed to find the parasites in the blood in the great majority of cases, and I have found this method of very little diagnostic value there. Mackie also gave up this method of diagnosis in Lower Bengal owing to its being very rarely successful there, although valuable in Madras. In the Mediterranean form a number of workers have recognized cases by finding the parasites in the blood, Vaglio recording 15 successes in 16 cases, and Wenyon in all 11 cases. In the Sudan D.S.B. Thomson and Marshall recorded 86·6 per cent of successes by this method.

The Cultivation and Development of the Flagellated Stage of the Parasite.—Up to July 1904 the only stage of the parasite known was the small oval body, about the size of a blood plate, with a rounded macronucleus and a smaller rod-shaped micronucleus or centrosome, such as are shown in the first line of Plate 7. These multiplied by division, so that in splenic smears a number of very small bodies may be seen in a single cell with no very definite capsule to them, but recognizable by the double nucleus; or a number of them might be found in a hazy material, first taken for a zoogloea mass, but now known to be but the protoplasm of the cell in which they were growing. It is not surprising, then, that there was much speculation as to the precise class of protozoa to which this organism belonged, suggestions varying from that of degenerated trypanosomes according to Leishman, the piroplasma of Donovan and Laveran, spores of a microsporidian of Christophers, and an entirely new genus which Ross put forward and proposed to call Leishmania-Donovani, in honour of the two observers who first described the parasite.

In 1904, a year after the announcement of the discovery of the parasite, I was fortunate enough to obtain multiplication and further development of the organism in cultures outside the body. The method employed was to obtain human blood containing the organism by means of splenic puncture, and to add it to about 1 c.c. of sterile salt solution containing 5 to 10 per cent citrate of soda to prevent the blood clotting, and to examine it frequently to see what became of the parasites. My first attempts were made at blood heat, with the result that they all died out in a day or two, as other workers had also found. Being struck with the resemblance of the macro- and micro-nucleus of the parasite to those of trypanosomes, just as Leishman had been, and remembering that Laveran and Mesnil had succeeded in keeping the latter organism alive for a much longer time at a low temperature than at blood heat, I next tried incubating the citrated blood at about 27° C., and found that in this way they lived for several days, and what is more, they appeared to multiply considerably, many dividing forms being present, but as yet without any other material alteration. On next reducing the temperature to about 22° C. (an ice incubator having to be used during most of the year in Calcutta for this purpose), I found that not only did the parasites unquestionably multiply rapidly, but they also increased in size and developed a blue staining protoplasm, and after a time the further development of flagellated forms took place, which were actively motile.

The different stages of this remarkable development are shown in the plate on the

opposite page, all the forms in which have been accurately drawn to the same scale with a camera lucida, thus illustrating the extraordinary increase in the size of the parasite as well as in its numbers. Whereas the human stage of the parasite appears to be no larger than a blood plate, and requires careful search with an oil immersion lens for its detection, yet the large rosettes shown in the lower part of the diagram can readily be seen as a stained mass, or in unstained specimens as a lighter circular area, among the red corpuscles with a $\frac{1}{2}$ -in. lens. The form in which the parasite is found in the human body is shown in the first line of the plate. The earliest stages of the development, which are shown in the second line, consist in an enlargement of the macronucleus, without any corresponding change in the micronucleus, which remains a small rod throughout the whole process. At the same time the protoplasm, which is clear in the spleen form of the parasite, now becomes much increased in quantity, and takes on a blue coloration with Romanowsky's stain, Leishman's modification of which was used throughout this inquiry. The next change is a curious one—the appearance in the protoplasm of a rounded mass which takes on the red element of the stain, and so may well be termed the eosin body; the micronucleus is always found to be closely attached to it while the flagellum arises from it. This form is seen in Nos. 3 to 6 of Line II., while the last two forms of that line show the flagellum arising from it, and apparently separated from the micronucleus by a narrow unstained space, although a study of degenerating flagellate forms proves that the flagellum is really organically connected with the micronucleus, for it comes away from the body with it, as shown in X. This flagellated stage rarely appears before the third day in successful cultures, and when the development is carried on under the most favourable conditions (to be described presently), they are found in enormous numbers, and showing all the stages of subdivision, which are illustrated in the third line of the diagram. In this process of multiplication of the flagellated forms the first change is the division of the micronucleus and flagellum into two, next the macronucleus also divides, and then a line appears down the centre of the body splitting it into two, the process being quickly commenced again by both the new forms. In this manner the rapidly dividing forms push each other round, as shown in IX., until they form a complete rosette of XII., the flagella all pointing in towards the centre, and in this stage such groups can readily be seen in fresh specimens by low powers with the flagella actively waving in the middle of the mass. Lastly, the individual forms, which up to now are mostly only two or three times as long as they are broad, gradually elongate out and begin to break away as shown in XI., to form single exceedingly active organisms, which when stained have the appearance shown in Line V., the eosin-staining micronucleus and flagellum being both situated at the anterior end of the organism, while the macronucleus still remains about the centre. The forms in Line VI. are the retrogressive stages of degeneration resulting from contamination of the culture with staphylococci. Forms VII. and VIII. show early development within a polynuclear leucocyte.

Now that extremely numerous, very active, and apparently fully developed flagellate forms have been obtained, without any tendency for the micronucleus to even approach the macronucleus and without a trace of any sign of an undulating membrane, it was clear that the parasite is not a partially developed trypanosome, but another kind of flagellated organism.

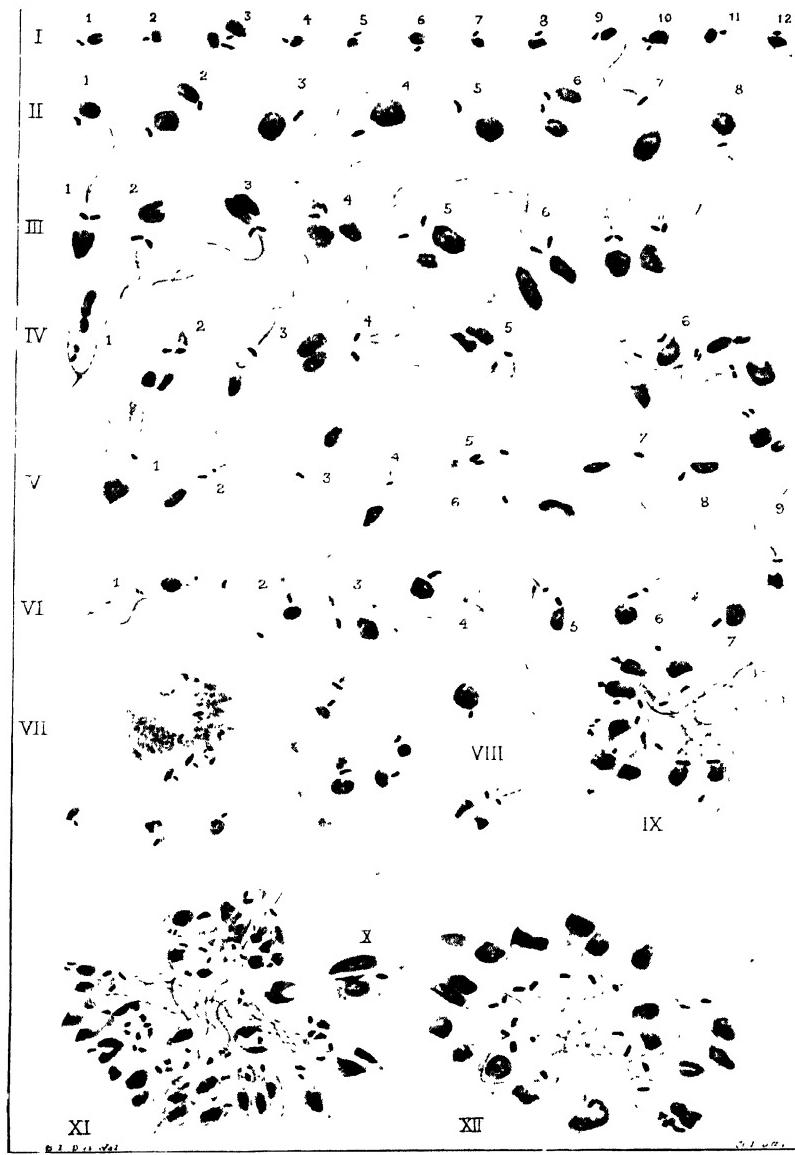


PLATE I.—Stages in the cultural development of the extra-corporeal stages of the parasite of Kala-azar.

- PLATE I.—
- I. Undeveloped parasites from spleen puncture film.
 - II. Early stages of development from two-days' culture in acidified blood; 1 and 2, body and macronucleus enlarged; 3 and 4, first appearance of eosin body; 5 and 6, elongation and subdivision; 7 and 8, first appearance of the flagellum.
 - III. Stages of division of the early flagellated forms.
 - IV. Double, long, swimming forms.
 - V. Fully developed long, free, active single forms.
 - VI. Degenerating forms.
 - VII. Undeveloped forms in a white corpuscle.
 - VIII. Early stages of development in a degenerating white corpuscle.
 - IX. Stage in the formation of a rosette.
 - X. Separated flagella with micronuclei attached.
 - XI. A dense cluster of parasites.
 - XII. Final stage of development.

The Nature of the Parasite.—My own impression was that the new flagellated parasite was an *Herpetomonas*, and Patton after carefully studying that genus in flies came to the same conclusion. It was, however, pointed out that, whereas the *herpetomonas* passes its whole life-history in insects, the parasite of kala-azar is principally a vertebrate one and probably only passes through insects in the course of its life cycle, and for this reason the suggestion of Ross, supported by Minchin, has led to a new genus, *Leishmania*, being created, and the parasite called *Leishmania-donovani* in honour of its joint discoverers. Later Nicolle suggested the term *Leishmania infantum* for the parasite of the Mediterranean form of kala-azar, but as the general opinion now is that it is identical with the Indian form that term is not required. The closely related parasite of oriental sore is termed *Leishmania tropicum*.

Conditions affecting the Development of the Flagellate Stage.—As the parasite only occasionally fully developed in my cultures, I carried out a long series of experiments to try to ascertain the most suitable conditions for the growth, in the hope of finding a clue to the probable mode of infection. In the first place the temperature limitations were found to be from 18° to 27° C., or about 60° to 75° F., from 20° to 22° C. being the optimum. Next sterility was essential, as if bacteria, especially staphylococci, obtained access to the cultures the protozoal parasite rapidly died out. Spagnolio subsequently confirmed this observation in the case of Mediterranean kala-azar, but found that the delicate *M. melitensis* was an exception, as it did not kill off the kala-azar parasite. Cornwall has come to the conclusion that bacteria act by exhausting the nutrient of the culture medium. Water quickly kills the organism, while I found that normal or slightly hypertonic saline was most favourable to the growth. The reaction of the medium was also of great importance, as it was not until I neutralised my citrate solution with citric acid that I obtained the most abundant growth, while this also sometimes took place in a slightly acid medium. This observation recalled to my mind some attempts I had previously made to cultivate plague bacilli from the stomachs of bed-bugs, in which I had been struck by the frequency with which their stomach contents were sterile, and while they were also acid even when full of human blood. This led me to suggest the bed-bug as a likely carrier of the infection, for by this time the Leishman-donovan bodies had been found in the peripheral blood, while the success of placing healthy coolies in lines only some two hundred yards away from infected ones made a flying carrier, such as the mosquito, very unlikely. In 1905 I visited Assam and examined microscopically the contents of the stomachs of over 200 bed-bugs caught in kala-azar infected houses for flagellates, but with a negative result.

My culture results were soon confirmed by G. C. Chatterjee working in my laboratory, and by Statham and Leishman and others, but the method was not suitable for making sub-cultures, and a further advance was made when Nicolle found the parasite of the Mediterranean form of kala-azar would develop well on Novy and MacNeal's blood agar medium and could be sub-cultured indefinitely on it. Longo and others also cultivated this variety of the kala-azar parasite by my method, while the Indian form has since been repeatedly grown on the Novy-MacNeal medium made with neutral agar and rabbits' blood, and the *L. tropica* of oriental sore also grows well in this way, having first been

cultivated by Row in Bombay. Nicolle found the following modification of the original medium best, and it is now known as NNN medium. Agar is macerated in two changes of water for twenty-four hours and 14 grams with 6 grams of salt added to 900 c.c. distilled water, dissolved and filtered and 4 to 5 c.c. distributed in small test-tubes and sterilized. After melting and cooling to about 55° C. one-third the volume of fresh sterile rabbit's blood, which may be obtained by drawing it from a rabbit's heart with a fine needle and syringe, and the tubes sloped and their sterility tested at 37° C. for twenty-four hours and kept from drying. Laveran and Pettit use a liquid medium made of 2 grams of peptone, 6 of sodium chloride, and 900 of water, 15 c.c. being placed in small Roux's flasks, an equal volume of defibrinated rabbit's blood being added and incubated at 22° C. Mathis has made an efficient sterilizable medium by using the NNN formula, but sterilizing at 80° to 100° C. on three successive days with the tubes in an inclined position. No differences have been found on culture between *L. donovani* and the parasite of the Mediterranean form of kala-azar, although that of *L. tropica* shows some points of distinction, as it flourishes at a higher temperature, such as 28° to 29° C., and is more resistant especially to bacterial contamination. Row also states that *L. donovani* is smaller and has a more distinctly pointed posterior end. Cornwall has described in bed-bugs a thick-tailed form with a flagellum four to five times as thick as usual.

An important practical outcome of the cultivation of the parasite is the proof that this can be done as a diagnostic measure from the peripheral blood in cases in which the parasites cannot be found microscopically, as first shown by Mayer and Werner, and soon confirmed by Wenyon. Cornwall has succeeded in 8 consecutive cases, although in some the blood was sent two days' journey to his laboratory, and one patient had no fever at the time it was taken.

Animal Infection.—The infection of animals with the parasite of kala-azar is a rather uncertain and usually of a scanty nature, so this method of research has not proved of much value in the elucidation of the problems presented by the disease, especially when compared with the results thus obtained in sleeping-sickness. The first successful work in this direction was recorded in 1908 in the case of the Mediterranean form of the disease by Nicolle in Tunis, who infected a dog by intrahepatic and intraperitoneal inoculation with the spleen blood from a case of infantile kala-azar, and soon after he also succeeded with a monkey, *Macacus sinicus*, the disease being usually a mild one. Laveran and Pettit have also produced very mild infections in rats, mice, and guinea-pigs. In the Sudan Marshall and Archibald infected two varieties of *Cercopithecus* monkeys. In India the earliest experiments with dogs gave negative results, but in 1912 Donovan reported the successful infection of a pup by intrahepatic injection of 3½ c.c. of kala-azar spleen blood, and Patton soon confirmed the observation, the earlier failures apparently being due to insufficiency of the dose of infective material. Row infected Indian monkeys, producing a local lesion in one, while Laveran infected a monkey in Europe with a culture of the Indian form of the parasite, and found that another monkey with immunity to the Mediterranean form was also immune to the Indian variety; thus strongly confirming the identity of the two forms of kala-azar. Mackie in India has also infected monkeys, flying-foxes, and white mice by intraperitoneal injection, but the results were very un-

certain, so the method is not reliable for attempting to prove the infectivity of suspected material. Feeding experiments were all negative. He found the common Assam domestic animal, cats, goats, and a young pig, to be immune against inoculation, but one of two jackals became infected.

The Natural Infection of Dogs in the Mediterranean area with a parasite indistinguishable even on culture from that of the human disease in the same parts is of great interest and importance. This was first found by Nicolle and Comte in Tunis in 1908, since which it has been confirmed in nearly all the countries bordering on the Mediterranean, the proportion of animals infected usually varying between 2 and 8 per cent, although occasionally higher. Evidence has also been produced that dogs in houses with human cases of kala-azar are frequently infected. Basille describes acute and chronic forms of the disease in dogs, and believes that the dog flea conveys the disease to children : a point which will be further discussed later. In India Donovan and Patton have each examined over 1000 dogs in Madras for the parasite with negative results, while Mackie in Assam and Wenyon in Bagdad also obtained negative results, which is the only important remaining difference between the European and Indian forms of the disease.

Insects and Kala-azar.—In 1907 Patton first obtained development of the *L. donovani* up to the flagellate stage in the alimentary canals of bed-bugs fed on kala-azar patients showing numerous parasites in their peripheral blood, similar to that which I had obtained in my cultures in citrated blood, and he subsequently found it to be most complete and extensive at the same temperatures as the optimum for cultures. Both *Cimex rotundus* and *C. lenticularis* were suitable for the experiment. He traced the changes through the flagellate to post-flagellate small oval forms, with different staining reactions to the human forms, and which he thought to be the infective stage, which might be regurgitated from the stomach in the act of biting. Wenyon disagreed with Patton's views, and considered that nothing more than cultural multiplication had taken place in the bugs, and no definite development of an infective form. Mackie in very numerous experiments did not succeed in getting any development of the flagellate stage in bugs, and failed to infect two monkeys either by injecting into them the contents of 815 bed-bugs previously fed on kala-azar patients ; while the dissection of over 1172 bed-bugs from kala-azar bed-coverings failed to reveal any kala-azar parasites in them. Similar experiments with large numbers of head and body lice were also negative, Patton having previously failed to get any development of the parasite in fed lice, mosquitoes, or ticks, while the *Conorhinus rubrofasciatus*, which Donovan had suggested as a possible carrier, also gave him negative results. Cornwall has confirmed the development of the flagellate stage in bed-bugs and showed they can live in them at least twenty-nine days, but he failed to get them to infect culture media bitten through rabbit's skin, and does not think their bites can convey the infection. However, he found two active flagellate forms in the rectum of a bed-bug, so it is possible that they may be passed in the faeces in an infective form, and that the contaminative method through the puncture made by the insect may be the mode of inoculation into the human subject, as suspected in the case of plague. It is clear that infection through bed-bugs has not been proved in spite of prolonged researches, while the fact that such development as has been demonstrated

usually only occurs when there are large numbers of parasites in the peripheral blood of the patient on whom the insects have been fed has been used as an argument against this being a true development of the parasite. On the other hand, we know that it is only in a small percentage of tsetse flies that human trypanosomes of sleeping-sickness develop into the infective stage, while I have pointed out that if such development was a frequent occurrence in bugs found in kala-azar houses it is difficult to see how any one could escape alive in the infected districts ; so greatly do bed-bugs swarm in Indian coolie huts that a very exceptional development would alone account for the epidemiological facts. Further search for other possible modes of infection is much required, but in the meantime prophylactic measures may well be especially directed against the one insect in which some development of the *L. donovani* has been demonstrated.

Fleas have been found by Bassile occasionally to harbour a flagellate which is difficult to distinguish from that stage of the parasite of the Mediterranean form of kala-azar, and he brought forward strong evidence to incriminate the dog-flea in carrying the disease from one dog to another, and considered that children were infected in the same way. Unfortunately he did not exclude the possibility of the flagellate being a natural one of fleas (which Patton did in the case of his bugs by using only laboratory-bred insects), and more recent work has thrown great doubt on his theory. Sergent, L'Héritier, and Lemaire have supported Bassile's work, while Wenyon and Da Silva failed to confirm him ; so this mode of infection is far from being proved and further investigations are required. Laveran, however, considers that there is strong evidence of the relation between canine and human kala-azar in the Mediterranean area, although wanting in India, so the destruction of infected dogs should not be neglected.

PROPHYLAXIS

Kala-azar is exceptional in so far that our knowledge of its prophylaxis, based on the author's Assam investigations, has for long been far ahead of that of the etiology. Thus the disease was successfully stamped out of tea-gardens in the Nowgong district by segregation measures, worked out by me, and carried out most thoroughly by Dr. J. Dodds Price, long before the parasite was even discovered, or the true nature of the disease understood, and they were subsequently also proved to be effective in the villages of the indigenous population. It has already been mentioned that I obtained strong evidence that the infection is a house, or at least a site one, and that a distance of a few hundred yards is sufficient to prevent the disease spreading from one group of huts to another for years, provided personal communication between the two is strictly limited. The first hint I got suggesting this plan was by learning that the Garos in the early stages of the Assam epidemic learnt by bitter experience that the best way to escape being more than decimated by the scourge was to move from their infected villages to a new site. I also ascertained that over a year before I went to Assam, Dodds Price, suspecting the disease to be infectious, had placed 150 out of 200 freshly imported coolies in newly built lines of houses, while the remaining 50 had to be accommodated in infected lines for want of room. I got him to work out the results of this measure. It was thus ascertained that

although none of the 150 in the new lines had suffered from kala-azar during two years they had been on this badly infected tea-garden, yet no less than 8, or 16 per cent, of those placed in the old lines were already dead of the disease, and that, too, in spite of the fact that the new lines were but 300 yards from the old ones, a distance insufficient to prevent the spread of malaria through the agency of mosquitoes.

This very important result obtained by Dr. Price encouraged me to suggest the further step of moving all the healthy people out of infected houses to new ones on a fresh site, no person, however, being taken from an infected hut in consequence of the impossibility at that time of differentiating the early stages of kala-azar from ordinary malarial fever. This plan was carried out by Dr. Price in the case of a coolie line which was so badly infected that no less than 144 out of 240 souls were either actually suffering from kala-azar or had cases in their households, leaving only 96 who could be moved to the new site, 5 of whom were very shortly afterwards sent back on account of their developing fever. A large number of fresh coolies were also drafted into these new lines, so that eighteen months later it contained 416 souls, among whom not a single case of kala-azar had occurred : a statement which happily remains true at the present time, ten years after they were occupied.

In marked contrast with this result is the fact that of 60 coolies, who refused to move out of the infected lines, no less than 20, or one-third, were attacked within the eighteen months, and they have since nearly all been carried off by the disease, although their houses were only 400 yards from the new ones, which remained healthy. This experiment was so conclusive that it has since been often repeated with uniformly good results, so that the disease is no longer as dreaded as it used to be by tea-planters in the Nowgong district. In slightly infected lines only the affected households were segregated and their houses burnt, this measure being also of value, although less effective than the former one. It is also of great interest to note that the new lines referred to were only situated just 400 yards from the old ones, in which the infection continued for years. Nevertheless the stringent precautions which were taken to prevent any infected persons visiting the new lines were sufficient for its permanent complete protection, which again points to some less active agent than the mosquito as the carrier of the infection.

In 1902 Dodds Price wrote to me regarding this crucial experiment : "Where the disease accounted for hundreds we never see a case, and even remittent fever hardly ever occurs. Here the most stringent measures were taken, and after a death-rate of over 10 per cent up to 20 per cent for several years, we only lost 9 souls last year out of a population of 500, and this year up to date (June 2) we have had only two deaths"—none of either year having been from kala-azar. In 1913 I visited the Nowgong district, and worked out with Dodds Price the results of these measures up to that date, and we recorded them in the following year. The accompanying table shows the results at a glance and demonstrates the absolutely uniform success of the measure in ten different places among a total working population of 6727 souls, not including numerous children, and over a period of eighteen years, which has now extended to well over twenty years. That the success was not due to the decline of the epidemic in the Nowgong district is shown by two facts. In the first place the outbreak at Seconee in 1908, when the disease had reached its minimum in the district, was just as severe as those at the height of the

FEVERS IN THE TROPICS

TABLE I.—ERADICATION OF KALA-AZAR FROM ASSAM TEA-GARDENS

Tea-Estate.	Working population.	Year of infection.	Deaths before the lines were moved.	Year of removal.	No. of infected left behind.	No. of infected who died later.	Distance the lines were moved.	No. of years the new lines have remained free.
New Rangamati .	622	1895	300 yds.	18 yrs.
Old Salona (Rangamati) . . .	800	1893	over 200	1897-8	140	fully 112	400 yds.	16 yrs.
Haspani . . .	625	1897	about 75	1899	over 100	at least 60	800 yds.	14 yrs.
Kondoli . . .	600	1892	over 150	1901	?	a few	..	12 yrs.
Kellydene . . .	900	1895	320	1902-3	about 160	about 75	750 yds.	9 yrs.
Amlucki . . .	1800	1896	350	1900-1	about 100	47	½ mile	13 yrs.
Lung Soong . . .	540	1902	about 35	1904-5	about 35	15	800 yds.	8 yrs.
Nonoi . . .	312	1893	about 85	1905-6	about 40	about 12	¾ mile	8 yrs.
Meesa * . . .	550	1896	over 50	1905-6	25	17	600 yds.	8 yrs.
Seconee . . .	678	1908	128	1911	98	23	600 yds.	2½ yrs.
Totals . . .	6727	..	1393	..	698	361
Deaths per mile	207	517

epidemic ten years before, showing that the aggregation of people in tea-garden coolie lines furnishes ideal conditions for the continual prevalence of the disease. In the second place, in the case of two important infected coolie lines the managers were so blind to their own interests that they refused fully to carry out the measures, and thus provided perfect controls, with the result that with the continued importation of fresh labour year by year the disease was kept up for twenty years in those two lines, and, although it had been checked for a time by partial measures, it was once more on the increase in one line and stationary in the other in 1913. After my visit in that year my measures were adopted, and two years later Dodds Price reported that these lines had been completely freed of kala-azar after having been infected for over twenty years, and they remain so to the date of writing (1918), so that Dodds Price for some time past has not been able to find a single case of kala-azar on any tea-garden in the Nowgong district among a population of some 10,000 people, including children. This is all the more remarkable as during the last few years the disease has shown a distinct increase in the indigenous population of this district, although nothing approaching that of the epidemic years. When we remember that the death-rate of the disease on tea-gardens, where accurate records are available, used to be at least 90 per cent, and the death-rates in some of the infected lines were originally from 100 to 200 per 1000 per annum, and showed no evidence of decline as long as the old system was continued of placing newly imported coolies in the old infected lines year by year, the above results in a disease the precise etiology and mode of infection of which is not yet fully known, is a triumph of preventative medicine which it would be hard to equal. That these measures are also applicable in the case of infected villages has been shown by McCombie Young, who records that among forty families moved to new sites from badly infected villages in Assam three years previously, a

recurrence of the disease in a person, not obviously infected upon the old site, has only occurred in one case, and that the people themselves recognized the value of the measures and were grateful to the Government for carrying them out. This evidence is of especial importance as indicating that the infection was left behind in the old site, because in the case of villagers it is not possible to segregate so completely the infected persons as in the case of tea-garden coolies, while at the same time it demonstrates that my measures can be applied equally well to the indigenous population. The measure adopted in the villages was to supply a new house with a separate sleeping apartment outside for infected members. The old house was burnt down, a point Dodds Price strongly insists on, and with it the clothing and other belongings which could possibly harbour insect parasites, liberal compensation being provided by the Government for the loss. These measures are now being carried out in the newly infected parts of the Sibsagar district, the importance of controlling the outbreak in which cannot be exaggerated.

CLINICAL DESCRIPTION

v

Having described the Assam epidemic of kala-azar and discussed its etiology and prophylaxis, I pass on to describe the disease itself, and shall show that it is not one whit less terrible whether considered individually or collectively, for it literally kills by inches after very prolonged sufferings. As the later stages are much more typical than the earlier ones it will tend to clearness if I first describe the characteristic advanced condition, returning later to the less easily recognized early stages of the fever.

The General Appearance in the Characteristic Advanced Stages of Kala-azar.—The typical condition in well-marked cases of kala-azar is well illustrated by the photo of a group of patients opposite page 20 (Plate 2), showing cases of the Assam epidemic disease in the Nowgong dispensary on a date in 1896 when the outbreak was at its height; while Plates 3 and 4 depict a series of the sporadic disease in Sylhet. The latter are of the more chronic type, and Plate 4 brings out the characteristic features most strikingly. The first point to note is the very marked degree of emaciation, as shown by the thin faces and arms and the prominent ribs. Secondly, in marked contrast with the general wasting, is the prominent tumid abdomen produced by the characteristically great enlargement of the spleen, and, to a less extent, of the liver. The feet may show dropsical swelling in advanced cases, but oedema of the face is very rare, and is only seen in the extreme last stages of the affection. It is the great muscular wasting combined with excessive enlargement of the abdominal viscera which constitutes the striking picture presented by these patients. The superficial abdominal veins often become distended.

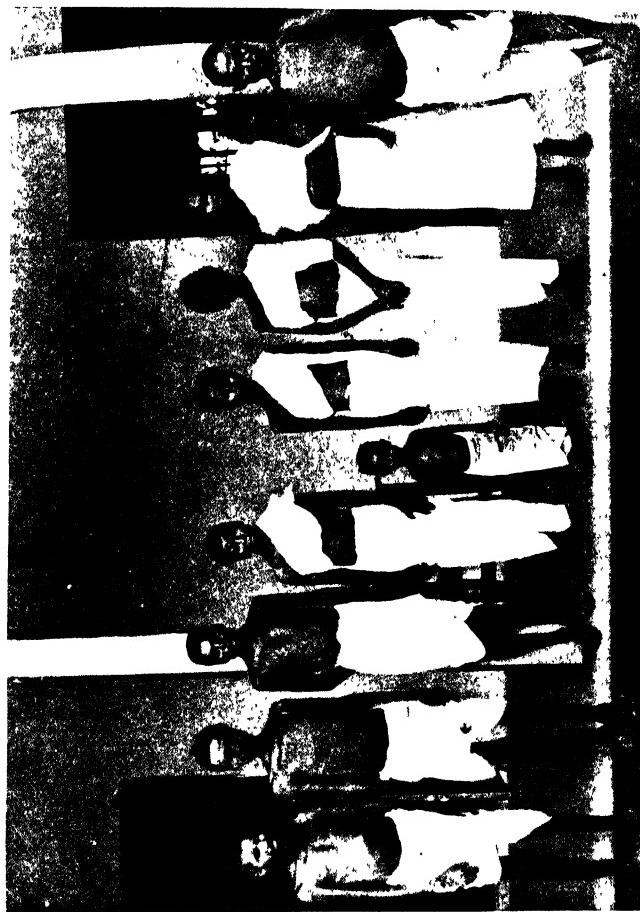
On examining more closely it will be noticed that the skin presents a peculiar dusky or earthy colour, from which the name of the disease (black fever) is derived, but this is difficult to fully appreciate at a single inspection in these dark-skinned races. It is only when a patient is seen again after several weeks' interval that this darkening of the skin is strikingly apparent; it is sometimes so distinct that at a first glance the patient may not be recognized as the same person. On examining the conjunctivae there is commonly little if any apparent anaemia, although it may sometimes become very noticeable in the late stages. Taken altogether the appearance in typical cases is so characteristic

that an experienced observer rarely fails to pick out a patient suffering from kala-azar at a glance in a hospital ward, although he may find it easier to do so than to describe in words his reasons for ~~so~~ doing. Plate 3 shows two very chronic cases which gave histories of six and ten years' fever respectively, and they show extreme enlargement of the liver and spleen. The group shown in Plate 2 is a very representative one as it includes all the cases in the Nowgong dispensary at the time it was taken.

Family Distribution.—The extraordinary tendency of this disease to attack a number of persons in the same family or household, and the frequency with which this is the case will be better realized from the following figures relating to twenty successive Assamese patients seen in the Nowgong hospital. Among their near relatives no less than 123 persons had been attacked by kala-azar, only 2 of whom recovered, while but 44 of their near relatives had escaped the infection; or to put it another way, no less than four-fifths of these patients had lost half or more than half of their relatives within three to five years, so that it is easy to understand how whole families have been destroyed, and so much land has fallen out of cultivation.

A similar family incidence is seen in the sporadic disease, and is best illustrated by a European series of cases, in whom it is easier to follow up the histories. An examination of my notes of the Calcutta European Hospital cases of the last six years shows that the most common relationships between patients actually in hospital for the disease were, parent and child in six instances, brothers and sisters in seven more, nearly always children, while in no less than three of these instances more than two children of the same household were admitted, the series in one family extending over a period of five years. Moreover, just one-third of the whole series of cases had relations actually in hospital during this period, while a good many more gave histories of other members of their families being attacked with fevers of long duration, which were pretty certainly of the same nature. This family incidence clearly points to a house infection, and was the main basis of the successful measures I advocated against the disease.

The histories of the rare cases in which Europeans in Assam were attacked by kala-azar throw some further light on this question, for in all the six cases, regarding whom Dr. Dodds Price kindly furnished me with information, the affected men were in the habit of cohabiting with native women either in the infected lines, or in three instances, each with a single woman, who was subsequently found to be infected with kala-azar. Two of these women eventually died of the disease. Two of these last cases of infection were most important, as they occurred in parts then uninfected with kala-azar, but in each case the woman had come from an infected district. Moreover, Dr. Price knows of no instance in which a European cohabited with an infected native woman and escaped kala-azar; and when we bear in mind that it is the usual custom for such women only to come to the bungalow at night and not to eat with the European, it becomes clear that the most likely mode of infection by a parasite occurring in the peripheral circulation is through some biting insect, in which the parasite may pass its extracorporeal stage of existence. Moreover, such a source of infection may furnish a clue to that of adult Europeans, with no family history to explain it, in large towns such as Culcutta, as well as among soldiers in Bengal cantonments, and this is also in accordance with the decreas-



PICTURE 2.—Group of cases of epidemic Kala-azar in the Nowrang Dispensary, Assam.

ing age incidence after early adult life. Again, the infection of one child after another in the same house may be also readily explained on the same hypothesis, and indicates the importance of isolating any person attacked by the disease, at least in a separate room, or better, in a hospital where persistent treatment and nursing can be carried out.

Age and Sex Incidence.—Among tea-garden coolies, who furnish the most accurate statistics, there was no difference in the incidence of the disease on the two sexes, nor did occupation affect it. Numberless instances of husband and wife being infected one after the other were met with, it being, in fact, the exception for one of them to escape—another striking instance of house infection. In the sporadic disease in Calcutta an excess of native males are admitted, much in proportion to those of other diseases. In the European hospital there were twice as many males as females above the age of 15, possibly partly due to the source of infection just mentioned ; but in children under 15 there were 23 females to 13 males, probably due to a larger proportion of the male children living away from home at schools. In China, Cochran saw only 4 females among 83 cases, males coming more for treatment. In infantile or Mediterranean kala-azar Nicolle saw 28 cases in boys and 17 in girls, while Jemma records 35 boys and 28 girls with the disease.

The age incidence is of great importance, the most striking fact being the number of children attacked. In my Assam report I recorded that 25·6 per cent of my cases occurred in children under 10, while 24·4 per cent more were between 10 and 20 years old, making 50 per cent under the latter age. Further, in a more recent report on the sporadic disease in Sylhet, 39 per cent were under 10, and 30 per cent more between 10 and 20, making nearly 70 per cent under 20. Among natives in Calcutta only 8 per cent were in children under 10, but 40 per cent between 10 and 20, three-fifths of which were boys from 10 to 15, who are much more readily brought to hospital than girls or younger children. Between the ages of 20 and 30 were 32 per cent, 16 per cent from 30 to 40, and only 4 per cent over 40 years of age. Among Europeans, who readily bring their children to hospital, 20 per cent were under 10, and 22 per cent more between 10 and 15, making no less than 42 per cent 15 or under ; 22 per cent from 20 to 30, and 20 per cent over 30, showing once more a very high rate among the unfortunate children, and a decreasing one with advancing years. In China, Cochran found 32·6 per cent of the patients to be from 1 to 10 years old, 29·6 per cent 21 to 30 years, 21·6 from 31 to 40, and only 3·6 from 41 to 50 years. In the Nowgong district of Assam in 1913 Mackie found among 195 cases 1 from 1 to 5 years, 100 from 6 to 10 years, 49 from 11 to 15 years, 17 from 16 to 20 years, 12 from 20 to 30 years, and only 8 cases over 31 years. In the Sudan the average age of Thomson and Marshall's cases was 12 years.

In infantile or Mediterranean kala-azar Jemma of Palermo records 63 cases, of whom only 5 were over 4 years of age, the eldest being 6 years.

Race Incidence.—It has already been mentioned that epidemic kala-azar was rare in Europeans in Assam compared with natives, but that it is not so very uncommon in Europeans in Calcutta in the sporadic form. The class of Europeans attacked in Calcutta is of great importance, for out of 87 cases, regarding whom I have a note as to how long they had been in India, I find that no less than 87·34 per cent were born and bred in that

country, and only 12·66 were immigrants from Europe. Moreover, the shortest time after arriving in India that any immigrant was attacked was eight years; a second had been thirteen years, and a third nineteen years in the country; while the remaining eight had all been over twenty years in India, and belonged to the same class as those born in Calcutta, and, like them, were living in parts of the city where their houses were surrounded by those of native inhabitants and under conditions of overcrowding and bad sanitation. In fact, almost all these unfortunate people belonged to the poorest sections of the mixed European and native population, among whom the sanitation and cleanliness of the well-to-do official and commercial European immigrant class is an impossibility—a fact of great importance in connexion with the etiology of the disease. In marked contrast with this is an observation I have recently made to the effect that 80 per cent of the European immigrants admitted to hospital for typhoid in Calcutta had been three years or less in India, for the totally different incidence of sporadic kala-azar just mentioned in this class will prove a useful point in the differentiation of the later disease, in its early remittent stage, from typhoid, with which it has been so much confused.

Seasonal Incidence.—Owing to the disease lasting from a few months to several years, cases are admitted to hospital at all seasons, and neither in Calcutta nor Madras is there any very marked seasonal incidence, although there is some excess of admissions of Europeans in Calcutta at the end of the cold and beginning of the hot season, especially among those coming in the early stages of the fever.

Of much greater importance is the question whether the fever begins at any special season, as is suggested by the fact that the extracorporeal stage of the parasite, to be described later, only developed in my cultures below a temperature of 75° F. It is very difficult to obtain accurate histories of the beginning of the disease in many cases, especially when they are seen for the first time at a much later date, but an analysis of my notes of those who stated they had had fever for not more than six months, in two series of cases (in the Native Medical College and European Hospitals respectively), showed, both, a marked preponderance commencing during the cold weather, or early in the hot weather, on account of the frequently long incubation period. These results can be summed up by saying that in the six months from November to April there were three times as many cases in the European series and almost four times as many in the native one as in the remaining six months of the year—a sufficiently striking fact when the difficulties of getting accurate data are considered. When in Assam I tried to work out this point from the admissions to hospital for fever on tea-estates, and found that most of the patients suffering from typical kala-azar in the cold season had been admitted for short attacks of apparently malarial fever in the previous rainy season from June to October, for but few escape malaria at that time. On finding that the sporadic cases in Calcutta mostly began in the cold season in Calcutta, I wrote to Dr. Dodds Price for his matured experience on the subject, and he very kindly sent me histories of all his European cases, every one of which had commenced in the cold weather; while an inquiry into his then comparatively few native patients also showed that almost all of them had developed kala-azar during the cold weather, and he added, “All this is very instructive, and fits in exactly with your Calcutta experience.”



PLATE 3.—Group of sporadic Kala-azar patients in Sylhet (Assam).

Taking everything into consideration, I think there is sufficient evidence to prove that the great majority of patients become infected in the cold season, and I am inclined to think that infection will ultimately be found to be limited to this time of the year. The importance of this fact in connexion with prophylactic measures is clear, as it will greatly simplify matters if precautions against infection have only to be taken during a few months of the year.

In connexion with the distribution of kala-azar in India already dealt with it is of interest to note that the areas affected all have a very mild cold season, during which the mean temperature for three or four months remains between 60° and 75° F., for I shall show later these are the limits between which I have been able to cultivate the parasite outside the human body. On the other hand, in the unaffected north-west parts of India the mean temperature during the cold months falls lower, while owing to the brevity of spring and autumn in India the temperature conditions most favourable to the organism outside the human body last a very short time in those areas. The absence of endemic kala-azar from the Bombay Presidency is not so easily explained on this ground although the cold season is a very short one, while the disease may never have gained a footing there.

Effects of Seasonal Variations on the Prevalence and Origin of the Disease.—I have already shown that the infection of kala-azar is probably limited to the cold season, so that an exceptionally long "cold weather" might be expected temporarily to increase the occurrence of the disease. This is actually the case, for some years ago such a cold season occurred, and during it and the following earlier hot weather months an unusually large number of sporadic kala-azar cases were admitted to both the native and European hospitals of Calcutta—many more than in the following year, with a normal cold season. Now this long "cold weather" followed an early cessation of the previous monsoon rains, for the withdrawal of the south-west monsoon is succeeded by a cold north breeze; and it has been mentioned that the Assam epidemic arose as a consequence of four out of five successive years of deficient rainfall in the early 'seventies, due to an early cessation of the monsoon current. I have not been able to get complete meteorological data for Rungpore in the 'seventies, but those of Calcutta of that period show without doubt that during several of the years of deficient rain the mean temperatures of the ensuing cold season were below the average.

Now, if a single cold year had such a marked influence in increasing the sporadic kala-azar in Calcutta, on account of the longer period which was favourable to the infection, it becomes easy to understand how an unusual succession of such seasons may have increased the number of cases, and in the same way the foci of infection, year by year, until the fever became so widespread that the people began to leave their villages, and thus carried the infection into areas at the foot of the Garo Hills and in the Goalpara subdivision, which had hitherto been almost, or quite, free from it, and so started the spreading disease in Assam in a people who were extremely susceptible to it, owing to not having previously suffered from the sporadic form. Such an origin of the Assam epidemic kala-azar is most in accordance with the known facts, and also with the life-history of the parasite and mode of infection, to be dealt with later.

THE TYPES OF FEVER IN KALA-AZAR

I now come to the difficult subject of the types of fever in kala-azar and their diagnostic value, which is very considerable when rightly understood, although they have not been hitherto fully worked out, especially as regards the early stages of the disease. As I have in my possession four-hourly temperature charts of all the cases admitted to the European Calcutta Hospital for some four years, and a still larger number from the native hospital, I have been able to study carefully the temperature curves at different periods of the disease. Further, for two complete years I possess the notes and charts of every fever case admitted to the open wards of the former hospital, including a number of early cases of kala-azar, which were subsequently followed up into the characteristic later stages, so that I am now enabled to point out the most important features of the temperature curves at the commencement and their differentiation from the charts of those fevers, which are most commonly confused with them. The following cases have been selected to illustrate the different stages of the disease and to demonstrate the features of the greatest diagnostic importance.

1. Child admitted in Advanced Stage whose Fever lasted over Six Months in Hospital before Death.—Chart 1, opposite page 26, illustrates the extraordinary power of resistance of children to this fever, as well as the terrible manner in which it drags out its slow course, only to be terminated by some complicating bacterial infection. The patient was a Calcutta-born European girl of six years, who had already suffered from fever for six months before admission, and was very thin and anaemic and did not look as if she would long survive. The temperature chart shows the great irregularity so characteristic of this disease, and also a tendency to waves of remittent fever alternating with that of an intermittent type, while in the month of September it showed for a time a distinctly continued type, which, taken by itself, bears a considerable degree of resemblance to that of typhoid, although in such a case as this the previous course of the affection is alone sufficient to exclude that disease. On looking more closely at the chart, which is a four-hourly one throughout, it will be observed that there is a marked tendency for the temperature to show considerable variations twice, or more rarely even three times, in the twenty-four hours; a feature I have already described under the term "double remittent type" as being frequently of great diagnostic value, and a chart of which I published as early as May 1903 as probably that of a new fever. This feature is well seen during the month of July, while it is specially noteworthy that it is also quite distinct during the continued typhoid-like curve in October, as I have not been able to find any case of true typhoid among my large collection of four-hourly charts in which such a double rise repeatedly occurred. Another common feature illustrated by her case was the occurrence of cancrum oris, the most frequent and fatal complication in children during this disease, which but few chronic cases escape. In this case it was of an unusual distribution as it affected the junction of the nose with the upper lip, producing a complete perforation, and after showing signs of healing it broke out again, destroying the rest of the lip, only again to cease spreading and once more to begin to heal. Another noteworthy and important practical point was that after the sloughing process ceased the patient, who had been



PLATE 4 - Two very chronic sporadic Kala azar patients

lying in an apparently dying condition for many days, greatly improved in her general condition, and within a very few days was walking about the ward, although still suffering from fever. This gradually subsided to the low intermittent form seen in November, but further recurrences of ulceration and fever ensued during the following month, and eventually in January she was released from her sufferings by an attack of pneumonia : a common and very fatal terminal affection. This case illustrates a number of the most frequent features of the latter stages of the sporadic affection.

2. Case of Seven Months' Duration followed from Beginning to End.—The next chart (2, opposite page 28) shows the case of another European girl aged seven years (whose father subsequently also died of the same disease) who was admitted on the sixth day of her fever according to the history obtained from her parents, with whom she was living at the time. The fever at first ran an irregular high remittent course, the spleen extended to only $1\frac{1}{2}$ in. below the ribs, and she was not wasted, so the case was very naturally looked on as one of typhoid fever. On seeing her chart some ten days after her admission, without knowing anything of the history, I noticed the double remittent type and at once suspected the case to be one of sporadic kala-azar, although the symptoms were certainly very like those of typhoid ; I therefore watched the case very closely. The temperature began to decline about the end of the third week, and the original diagnosis of typhoid seemed about to be confirmed. Instead, however, of remaining normal, or showing the sub-normal curve of early convalescence from typhoid, the temperature continued to rise a degree or two every evening, as is so frequent at times in the course of kala-azar. This daily low fever rising to about 100 in the afternoon, and falling again to normal in the night lasted just one month, to terminate in another high wave, during which the double daily remission was again apparent for a few days, and was again succeeded by a less regular intermittent fever with occasional double daily variations. Early in September she was sent to Darjeeling, at a height of 8000 feet above sea-level, but the irregular intermittent fever continued, and in the middle of October she returned to the Calcutta hospital with her general condition worse than before she went to the hills : this change having been (as we usually find) quite ineffectual in checking this fever. In December she became much worse, the temperature now assuming the continued type, which is more common in these later stages than in the earlier ones. In January she was attacked with dysentery, which quickly proved fatal : this being another common terminal complication, although more frequently seen in native than in European patients.

This chart illustrates the disease from beginning to end, and is of great interest in showing the similarity of the disease to typhoid in the early stages, and as illustrating the two most important differences from the temperature curve of that disease, namely, the double remittent type appearing very early in the disease, its course, as well as the low intermittent fever following the decline of the high initial remittent pyrexia.

3. Double Remittent Type of Early Kala-azar Fever mistaken for Typhoid.—Chart 3 is that of a man admitted early in May with a typically double remittent type of fever passing into a high remittent pyrexia. He gave a history of having been treated for typhoid fever in March, and on obtaining his temperature chart of that attack it also

FEVERS IN THE TROPICS

showed the double remittent form for several days, as seen in the early part of the illustration. I had no doubt he was suffering from an early stage of sporadic kala-azar, which,

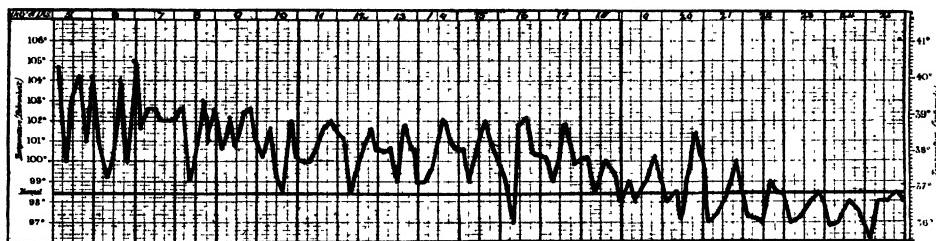
CHART 3 (Caso 347)



Early Kala-azar showing double remittent fever passing into a high remittent type, which gradually fell to a low remittent form. On admission a blood count showed 4,010,000 red corpuscles, 1750 white; ratio of white to red, 1 to 2291. Total polynuclears, 875; differential count, polynuclears, 50·4; lymphocytes, 35·6; large mononuclears, 12·4; eosinophiles, 1·6 per cent. Note the characteristic relative reduction of the white corpuscles

unfortunately, subsequently proved to be the case. It is quite a common event for patients in a typical stage of kala-azar to give a history of having suffered from typhoid

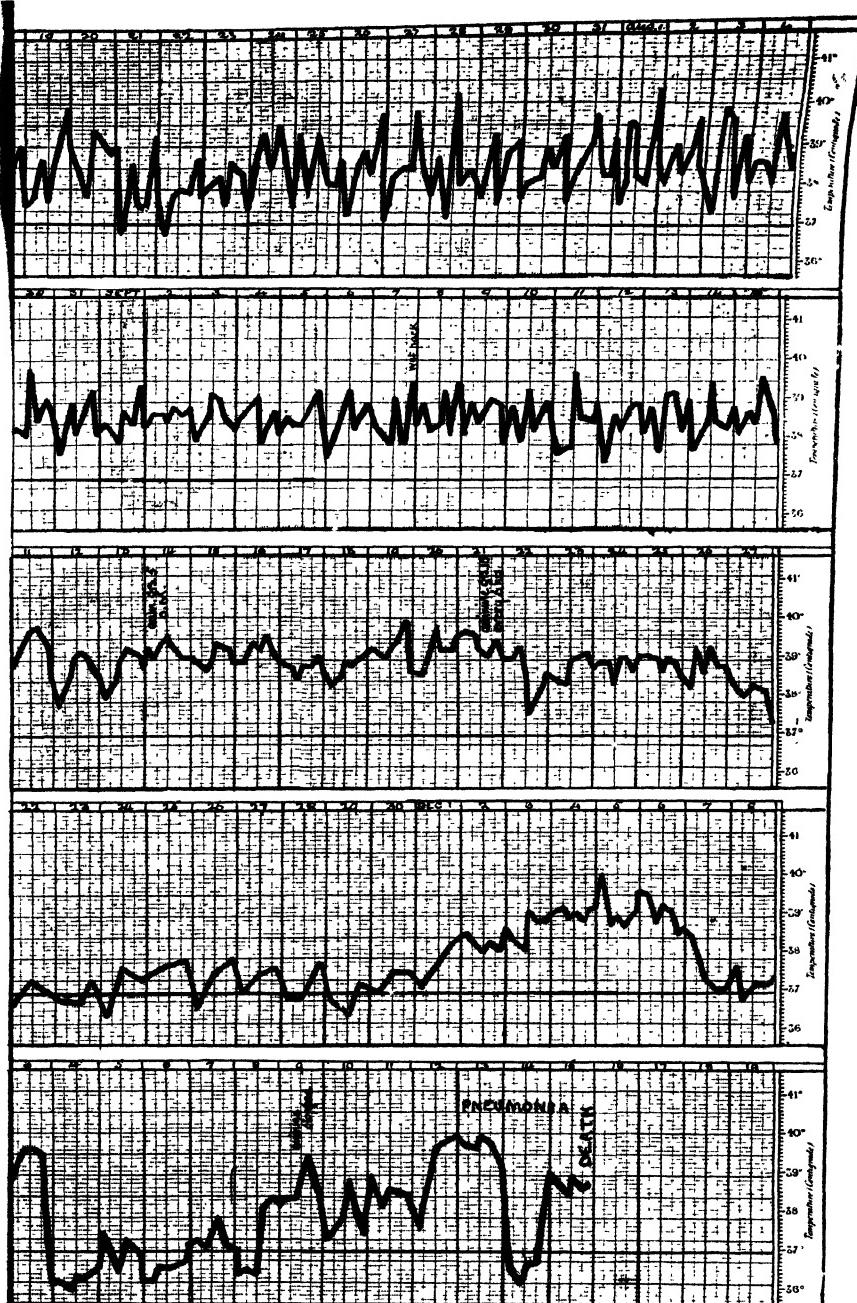
CHART 3A



From the same case as Chart 3 during an attack of fever two months before admission, which was mistaken for typhoid, but shows the double remittent type of pyrexia.

some months previously, but when a record of the attack is available it will almost always be found that the temperature did not show the high continued type of typhoid (see p. 104).

4. Double Continued Fever in Early Kala-azar diagnosed as Typhoid.—A still more difficult case is that shown in Chart 4, for here is seen a high continued pyrexia (that is, a temperature remaining persistently above 101, and with a diurnal variation not exceeding 2° F., for two or more days); this I have found to be very characteristic of typhoid fever (see p. 104). Moreover, the fever terminated by lysis at about the end of the third week, and was very naturally returned as typhoid. The patient was a European boy, aged thirteen, the brother of two other patients admitted at different times for somewhat similar attacks each diagnosed as typhoid, although I was unable to get any serum reactions in them during their fever. All three subsequently developed great enlargement of the spleen and other typical symptoms of sporadic kala-azar. One, a girl of eight, eventually completely recovered and remained well up to four years later when last seen; the second, a young lad, died of the disease after eighteen months; and the boy whose chart is given was repeatedly in hospital during the next two and a half years



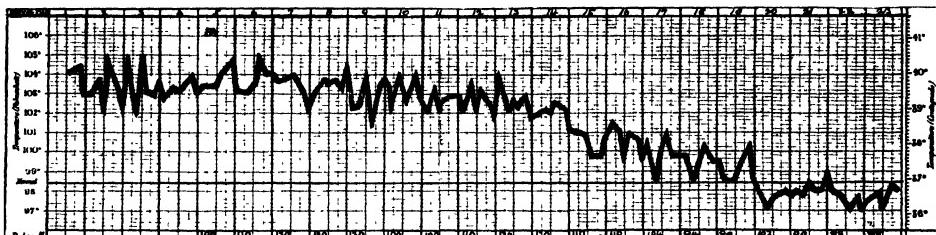
is in the twenty-four hours, occasional high continued pyrexia, complicated in the end

with an enormously enlarged spleen and intractable fever, and died at the end of that long period of suffering.

On carefully examining the chart of his first typhoid-like attack, it will be seen that there is marked tendency to the occurrence of two rises in the course of the twenty-four hours. *This I have never seen in undoubted typhoid or other fever, and I am compelled to regard it as practically pathognomonic of kala-azar.* The great diagnostic value of these double rises is that they so very frequently occur in the early stages of the disease, when there are no other characteristic features present, although they may appear at any time in its course. In one case, which I treated for three months with large doses of quinine, during which the patient had only low intermittent fever and was steadily improving, as soon as the quinine had been reduced to only 5 grains a day by another medical man, the temperature began to rise much higher and a typical double remittent curve appeared.

Another feature of this early stage of kala-azar is the slightness of the general symptoms in comparison with the high degree of fever, the entire absence of marked

CHART 4



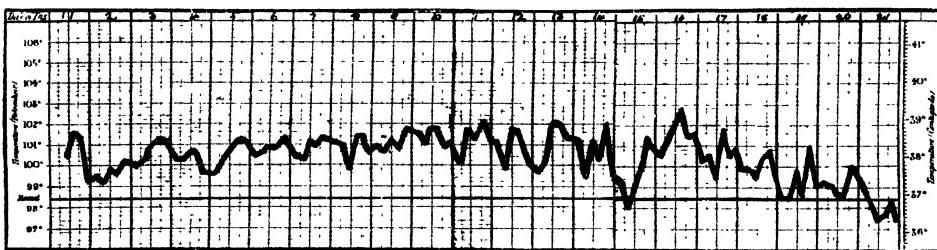
Early stage of Kala-azar admitted with high continued fever, which was diagnosed as typhoid, but showed double daily rises repeatedly; he returned later in a typical condition of Kala-azar. The case was followed up to his death after two and a half years.

mental dulness and delirium, and usually of any urgent and distressing symptoms, or of abdominal distension or tenderness, thus presenting a great contrast to the common condition in typhoid fever; this point has also been noted by T. H. Symons and A. T. Long in Madras (Madras General Hospital Reports). In fact, numerous cases of early kala-azar are very frequently regarded as typhoid fever.

5. Early Kala-azar with Low Continued Fever; suspected to be Typhoid.—Chart 5 shows yet another type of fever, which is commonly seen in the course of kala-azar, and which is also of considerable diagnostic importance on account of its much greater rarity in typhoid and other fevers. This is what I call the "low continued type," in which the temperature falls below 101, but with a diurnal variation not exceeding 2° F., without however, falling to normal. It is well seen in the first part of Chart 5, which was that of a European, aged fifty-two, who had lived for fifty years in India. On admission to hospital his spleen was only just felt, and he was not anaemic. His blood was repeatedly tested by a Widal reaction, with negative results, while the large mononuclear leucocytes numbered 12.4 per cent, which is a higher percentage than is found in early typhoid fever. As there was still some doubt about the case I took some blood from a vein with a sterile

syringe and made cultures in a quantity of broth, but no typhoid bacilli were grown, so I strongly suspected the presence of an early stage of sporadic kala-azar. His temperature fell to normal on the 31st day, and he soon after went for a river trip, but four months later he returned to hospital, giving a history of having suffered from fever on and off since his previous discharge, and showed a marked enlargement of the spleen and the typical blood changes of kala-azar, which ran a somewhat rapid course, as is frequent in comparatively old patients. He died from terminal dysentery four months later. In

CHART 5



Early Kala-azar, showing low continued pyrexia, thought at first to be typhoid.

this case it was the low continued type of fever which made me suspect the disease in its early stage.

6. Recovery from an advanced Stage after Complication with Cancrum Oris.—The next case is a very remarkable one illustrating the occasional recovery which may occur from an apparently absolutely hopeless condition (see Chart 6, opposite page 30). The patient was an Indian-born European girl of eight years, whose sister had recently died in hospital of the same disease. She was admitted with a history of one month's fever, but her spleen already reached to the level of the navel and her liver 2 in. below the ribs. She was markedly anaemic, her red corpuscles numbering 2,875,000 and the white only 1375, or a proportion of 1 white to 2091 red : this *marked relative leucopaenia I have shown to be practically diagnostic of the disease and to be of bad prognostic significance*. As will be seen from the chart, the fever ran a long course with the usual alternations of the remittent and intermittent types, the latter preponderating. During the temporary cessation of the fever late in December and early in January she improved considerably, and the white corpuscles increased to 4500, only to fall again during the high continued fever early in April to less than half that number. At this period she developed cancrum oris affecting the nasal passages and was moved into the separation ward in such a condition that her death was daily expected, a large abscess having also now developed over one hip. To the surprise of every one, a few days later the temperature began to fall once more, and she sat up in bed and began to play with her toys, as though she had risen from the dead. On April 25, just two weeks after the temperature began to decline, I found her leucocytes to number 8625, just four times the number found three weeks before, while the differential counts showed that the total number of polynuclears had risen from 132 to 2242 during the same period, a

most remarkable change brought about by the septic complications she had been suffering from. She continued to get slight intermittent fever for several weeks longer, then a low rise to about 100° F. for another month, after which her temperature remained normal. She gained weight rapidly, became quite fat, and returned to school in July, where I saw her in the following December the picture of health six months after her fever left her, so that she may safely be regarded as having completely recovered.

This recovery, after some septic complication, is by no means very exceptional, several other similar cases having come under my observation. Moreover, in at least three instances, in which numerous parasites had been found by spleen puncture within a few weeks of the death of the patient from cancrum oris, or some other septic infection of either staphylococcus or streptococcus origin, the parasites have been found post mortem either to have decreased to such an extent as to be only found in the bone marrow after some search, or to be altogether absent. Thus there seems to be some ground for thinking that the septic intoxication is highly inimical to the life of the protozoal parasite of kala-azar, just as the presence of bacteria is fatal to the development of the parasite in culture. This would seem to indicate a possible line of treatment for this highly resistant form of fever. The case further shows that no case is too desperate to recover.

7. Early Case successfully treated by Perseverance with large doses of Quinine.—The last chart (No. 7, opposite page 32) is of great interest. It is that of a European girl of eight, the sister of two advanced cases of the disease, who herself was brought to hospital two weeks after her fever was noticed. At this time her spleen already reached down to the level of the navel, indicating a long incubation of the disease. She remained in hospital for 286 days; by this time she had been quite free from fever for 4½ months and had fully regained her weight, while seven months later I heard from her mother that she was still in perfect health. Her chart shows the usual variations in the temperature curve, while towards the end of November she was much wasted and presented the typical appearance of advanced kala-azar. Up to this time she had been taking from 36 to 40 grains of quinine steadily, and it will be seen that her temperature kept at a lower general level than in most of the other charts, especially those of children. On December 6, the quinine was increased to 50 grains daily in 10-grain doses, a very large quantity for a child of eight, there being commonly a remarkable tolerance to this drug in kala-azar. A few days later the temperature began to decline, and from that time she steadily improved, the same doses of quinine being continued for nearly two months and 30 to 40 grains being given a day for a further period of three months, by which time she had completely recovered, and become very well nourished. Her weight is shown week by week in Diagram IV. together with the doses of quinine and the type of the fever, and illustrates very well the relationship between the waves of high remittent fever and the wasting, and the improvement as soon as the temperature falls again to a low intermittent type. It is the power which large doses of quinine appear to possess of breaking the high remittent pyrexial waves (during which both a marked loss of weight and blood deterioration always occur) and bringing the curve down to a low intermittent form (during which equally steady general improvement commonly takes place) which makes it so valuable a drug if pushed and persevered with. It is at least clear in the case of this child that

the relatively enormous doses given did no harm before the curative effects of antimony preparations was discovered.

The above cases will serve to give some idea of the extraordinary length and variability of the temperature curve, and how this makes the disease extremely difficult to describe systematically. The general symptoms in the earlier stages are so indefinite

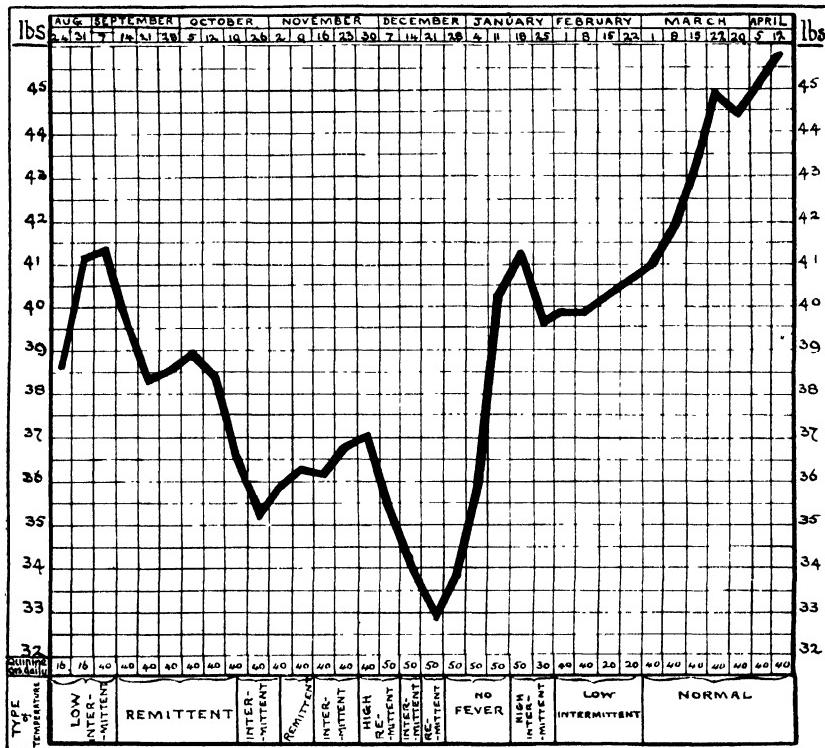


DIAGRAM IV.—Weekly weight chart of Kala-azar, Case 7.

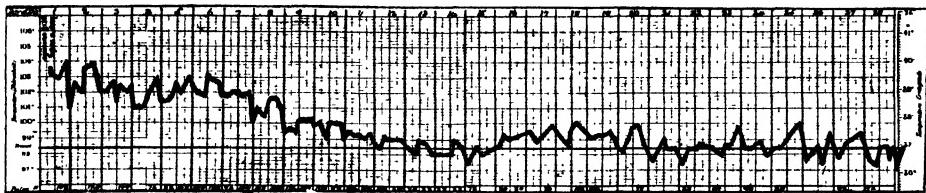
that it is only by careful watching and the gradual exclusion of typhoid, malaria, etc., and above all by the blood changes, described on p. 12, that they can be recognized.

The Frequency of different Types of Fever in various Stages of Kala-azar.—The cases already described illustrate the variability of the pyrexia in the course of this prolonged fever. The frequency of the types are shown in Table II., the cases being classed in accordance with the duration of the fever, and also subdivided into those in which the spleen was not enlarged down to the level of the navel, and those in which it extended to or beyond that point. The latter cases cannot well be mistaken for any disease except true chronic malaria, which is easily recognized by the parasites and the effect of quinine in rapidly controlling the fever. The first class of cases is often much more difficult to differentiate.

from typhoid and other long fevers. The following are the most important points illustrated by the table. As the same case may show different types at different periods the most constant or striking feature has been used for classification.

The high continued type includes only 10 cases, or 12 per cent of the series. In only 2 of them, however, was the spleen not enlarged down to the navel, both being within the first month. One of them was recognized at once as early kala-azar by the fact that the

CHART 8



Early Kala-azar. showing the rare high continued pyrexia, and mistaken for para-typhoid on account of a positive serum reaction. The patient later became a typical Kala-azar, and was followed up to his death.

white corpuscles were under 1 to 3000 red, but in the other the total leucocytes were not counted, and I mistook the case at first for para-typhoid as a serum reaction up to 1 in 40 was obtained with the *B. bacillus*, although typical kala-azar subsequently developed and proved fatal (see Chart 8). Again, the high remittent type was only observed in 5 cases, 2 of which had comparatively small spleens, but in 1 this was due to the effect of diarrhoea, and only 1 was in an early stage when typhoid might have been suspected. In this case, once more, the ratio of white corpuscles to the red was under

TABLE II.—THE TYPES OF FEVER IN VARIOUS STAGES OF KALA-AZAR

	High Con- tinued.	Double Re- mittent.	High Re- mittent.	Low Re- mittent.	Low Con- tinued.	High Inter- mittent.	Low Inter- mittent.	Total.	Grand Total.
Spleen above Navel.			Spleen above Navel.	Spleen above Navel.	Spleen above Navel.	Spleen above Navel.	Spleen above Navel.		
Spleen to Navel.			Spleen to Navel.	Spleen to Navel.	Spleen to Navel.	Spleen to Navel.	Spleen to Navel.		
1st month	2	1	9	2	1	..	1	1	26
1-3 months	4	..	2	..	1	2	..	14
3-6 months	1	1	3	..	1	..	3	13
6-12 months	1	2	2	2	4	16
Over 12 months	1	..	1	2	..	1	1	14
Total	2	8	12	9	2	3	2	3	83
Percentage	12.1	25.3	6.0	13.2	6.0	10.9	26.5		

1 to 3000, which enabled kala-azar to be diagnosed within the first month of the fever. If we take both the high continued and high remittent types together we still find only

4 cases, or 5 per cent of the whole, which might clinically have easily been mistaken for typhoid and in at least 2 of these the blood count at once excluded that disease. *The importance of this fact is that over 80 per cent of typhoid cases show these high degrees of pyrexia, mostly of the continued type, so that their great rarity in early kala-azar is of extreme value in differentiating between these two much-confused diseases.*

Next the frequency of the double remittent type in kala-azar is shown in the table to have been present in one-fourth of the total cases during their stay in hospital, which

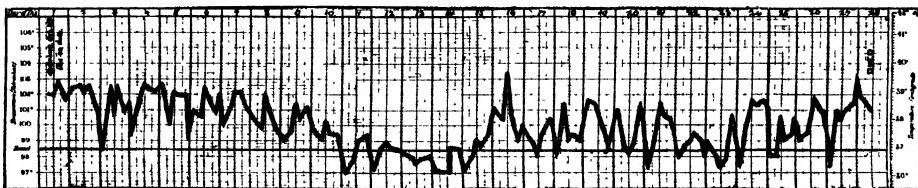
CHART 9



Fairly early Kala-azar, showing irregular double remittent fever passing into high continued pyrexia.

was often a comparatively short one. Moreover, four-sevenths of them belonged to the difficult group without great enlargement of the spleen. Further, it occurred in one-third of the patients admitted within the first month of the fever, and in almost one-half of the early cases without much splenic hypertrophy : that is, it occurred in just the most difficult cases of all to recognize. *Now this double remittent, or rarely double continued, type I have never met with except in kala-azar*, and occasionally in acute amoebic hepatitis, when the accompanying leucocytosis will exclude kala-azar, so that the great diagnostic value of this sign in early kala-azar becomes clear, and can hardly be exaggerated. It has frequently enabled me to correctly recognize these cases when no other characteristic

CHART 10



Kala-azar showing a low remittent temperature passing into an irregular intermittent one.

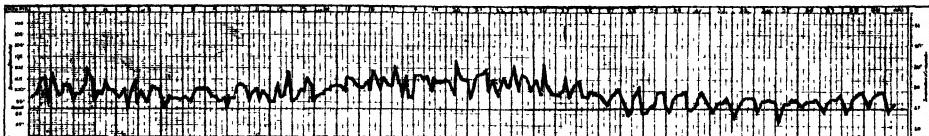
clinical signs (apart from the blood counts) were present, and has never yet misled me. Chart 9 shows the double remittent type passing into a high continued one.

The low remittent type predominated in the 11 cases, but only 2 of these were doubtful ones with small spleens, 1 being early recognized by the presence of marked leucopaenia, the other being suspected owing to a sister being in hospital with typical kala-azar at the same time. Chart 10 shows such a case in which the parasite of kala-azar was found by spleen puncture after death.

Only a few cases are classed as of the low continued type, but several of those classed under other heads showed this type at later dates, while it may sometimes be present in the early difficult stages as in Chart 11.

The number with a low intermittent type, that is, not rising above 101, and often not over 100, for days together, is striking, but they are mostly late typical cases with very large spleens, such as are readily recognized clinically, while this type is rarely met with

CHART 11



Early stage of Kala-azar, showing low continued pyrexia followed by low intermittent fever, and ending fatally several months later.

for long in other tropical fevers, with the exception of the low fever of Europeans described on p. 205.

Although, then, the types are very variable, they are nevertheless of considerable diagnostic value, for they rarely simulate typical typhoid temperature curves, and often show the characteristic double diurnal variation of kala-azar, or the low continued and intermittent types, which are far more common in this disease than in any other fever. Taken with the blood changes described below, they will almost always enable the disease to be recognized in quite its early stages, when antimony treatment is most effective.

GENERAL SYMPTOMS IN KALA-AZAR

It has already been mentioned that in its early stages the most striking thing about kala-azar is the persistence of high fever with very little general constitutional disturbance or physical signs. The following data derived from an analysis of the large European Hospital series of cases in all stages of the affection will best illustrate the commoner symptoms.

Rigors.—In a large proportion of the early cases a history of rigors is obtained, usually coming on daily at the beginning of the disease. In the later stages they are much less commonly met with, and may be altogether absent, and it now becomes common for a patient to say he feels quite well and has no fever, when the clinical thermometer registers anything up to 103° or 104° F. Occasionally in the early stages a history may be obtained of two rigors within twenty-four hours, while the occurrence of a double rise of temperature is often remembered by the patient, and may be an important point in suggesting the nature of the disease.

Headache.—This symptom was only noted in about one-fourth of the cases, being less frequent than in any other form of fever in the tropics, and seldom of severe degree. It was more often noted in early than in late cases.

Sickness was also seldom present, being only recorded in one-seventh of the series, being thus much rarer than in malarial fevers, while nausea was also very uncommon.

The Lungs were quite normal in almost 90 per cent, but pneumonia occurred in 4 per cent, usually as a terminal complication. This may be accompanied by pleurisy ; phthisis also occasionally supervenes in chronic cases. Bronchial râles are rarely met with, and are especially uncommon in the early typhoid-like stages. In the advanced cases some bronchial signs were present in about 10 per cent.

The Heart in the later anaemic stages frequently shows haemisystolic murmurs, but rarely any other complication. The **pulse** rate is nearly always considerably increased during fever, and very seldom shows the slow rate of under 100 a minute with a temperature of 103 and over, as so often seen in typhoid. Mackie lays especially stress on a rapid pulse as of diagnostic importance.

The Bowels in the early stages are commonly regular or somewhat constipated, but diarrhoea at times was recorded in one-sixth of them. In the later stages bowel complications are much more frequent, and they are often of a severe and intractable nature. In one-third of the cases diarrhoea occurred while in hospital, and in 7 per cent more dysentery was present. In native patients this last serious complication occurs much more frequently than in Europeans, and often causes a fatal termination. With looseness of the bowels the size of the spleen may become greatly reduced.

The Abdomen is nearly always normal in the early stages, with the exception of enlargement of the spleen. Distension was very rare in them, thus contrasting with its great frequency in typhoid. In the later stages some distension or tenderness was recorded in one-fifth of the cases, usually in connexion with bowel trouble, especially dysentery, but it was usually slight in degree.

THE SPLEEN AND LIVER

It is not until we come to the great vascular abdominal organs that we meet with the most characteristic organic changes in kala-azar. These are—great, often extreme, enlargement of the spleen, and to a less extent of the liver ; this is the most constant feature of the typical stages of the affection, and the former organ is often much increased in size even in the early fever.

The Spleen.—The following data illustrate the size of the spleen in kala-azar. In 70 typical cases of the epidemic disease in Assam this organ was enlarged in all. In no less than 94.5 per cent it extended to at least 3 in. below the costal margin, in 56.5 per cent it reached to the navel or beyond, while in 27.7 per cent the lower border was down to at least the level of the anterior superiors spine of the ilium ; in some of these cases it reached the pubes. In 95 cases of the sporadic form of the disease in Calcutta, mostly in natives, and all verified by finding the parasite by spleen puncture, this organ reached to the level of the navel or below in 80 per cent, while in 10 per cent it extended to the level of the anterior superior spine of the ilium. Nearly all these cases were in a fairly advanced condition, and readily recognized clinically as either kala-azar or malarial cachexia.

The degree of enlargement of the spleen and liver in different stages of kala-azar can be studied in Table III., showing the data of the earlier European Calcutta Hospital cases classified in accordance with the duration of the disease at the time of admission.

It is clear from this table that there is a progressive enlargement of the spleen throughout the course of the disease, for whereas in nearly two-thirds of the cases admitted with a history of less than one month's fever the organ did not extend more than 2 in. below the costal margin, yet in only one-seventh of those admitted after three months was the spleen as small as this, while in 37 out of 47 it reached as far as the navel. In only 4·3

TABLE III. ENLARGEMENT OF LIVER AND SPLEEN AT DIFFERENT STAGES OF KALA-AZAR

	Under 1 Month	1-3 Months	3-6 Months	6-12 Months	Over 1 Year	Total	Percentage
I. SPLEEN.							
Normal	4	4	4·3
Just felt	6	1	1	1	..	9	9·7
1-2 in.	8	4	2	2	..	16	17·2
2-4 in.	..	1	1	2	1	5	5·4
To navel	4	6	1	..	3	14	15·0
Below navel	7	5	9	13	11	45	48·4
Total	29	17	14	18	15	93	..
Percentage	31·2	18·3	15·0	19·3	16·2
II. LIVER.							
Normal	22	6	5	2	2	37	41·1
Just felt	1	3	2	1	3	13	14·5
1-2 in.	2	3	4	6	4	19	21·1
2-4 in.	1	2	2	3	5	13	14·5
To navel	..	2	1	3	2	8	8·9
Total	26	16	14	18	16	90	..
Percentage	28·9	17·8	15·6	20·0	17·8

per cent of the total was the spleen not palpable below the ribs, these all being cases of under one month's duration, which were subsequently followed up into the typical stages.

Another striking feature is that in 11 out of 29 patients with a history of less than one month's fever the spleen nevertheless reached to or below the navel. In some of these there had probably been earlier fever which was not recorded, but this will not explain all of them, and it is certainly not rare for a patient to come for recently commenced fever, and yet to find the spleen very greatly enlarged. The disease may thus undoubtedly begin very insidiously with little or no fever at first, and thus the incubation period may be prolonged, and the date of infection be actually some time before actual pyrexia becomes evident. In this respect it differs from true malarial cachexia, in which a history of

repeated ague will invariably be obtained, as far as my experience goes. It is also noteworthy that even in this comparatively early series the spleen extended down to the navel in 63 per cent.

The organ is usually hard, and in very chronic cases its firm edge may project so as to be evident to sight through the abdominal wall. In earlier cases, especially during high fever, it may be softer, in which case some care is necessary before puncturing the organ is undertaken. It may also vary rapidly in size from week to week in the earlier more acute cases, increasing with high remittent pyrexia, and decreasing with low intermittent fever. Still more striking is the way in which an apparently chronic and very hard spleen, reaching to below the navel, or even to the pubes, will entirely disappear once more beneath the ribs within a few months of the final cessation of the fever, the patient at the same time recovering his strength and becoming particularly well nourished instead of being a living skeleton. Such cases never relapse in my experience, or in the much larger one of Dr. Dodds Price in Assam, but as long as the organ remains much enlarged and low fever and emaciation persist, so long is the patient in danger of an acute exacerbation of the pyrexia or the supervention of some fatal complication. Dodds Price has recently reported a number of cases of fatal kala-azar with little or no enlargement of the spleen, so the disease cannot be excluded on that ground.

As a former writer on epidemic kala-azar has stated that it would be absurd to attach any importance to enlargement of the spleen in kala-azar in such a malarious country as Assam, it may be well to add that among 200 healthy coolies on a most malarious tea-garden (which, however, was free from kala-azar), I found only 1 per cent with spleens down to the navel, 6 per cent with spleens extending 3 in. below the ribs, and in just one-fourth of the whole some degree of enlargement—figures which effectually disprove that contention.

The Liver.—This organ was enlarged in 43 per cent of my Assam cases, in 75 per cent of the more chronic sporadic disease at the Calcutta Medical College Hospital, and in 59 per cent of the earlier European Hospital series. The size of the organ in different stages of the disease in the last series is shown in the second part of Table III., which well illustrates the progressive enlargement with the progress of the affection. Thus during the first month it was nearly always normal, and never very greatly hypertrophied, in spite of the fact that the spleen often reached the navel in these cases, while after six months it was increased in size in over nine-tenths of the cases, and not very rarely reached the navel.

The liver is usually firm, and becomes very hard in the more chronic cases. In those which last for two or more years, as is not very rare in the sporadic disease, an actual cirrhosis of the liver may ensue, of a very peculiar type, which I have described under the term intralobular cirrhosis. It is characterized by an absolutely smooth surface to the organ, but on section the liver is found to be exceedingly tough, and so firm that digital pressure has no effect on it. Microscopically it shows a very diffuse intracellular cirrhosis, in the fibro-cellular tissue of which shrunken parasites of kala-azar may still be visible with a high power. The liver cells are extremely atrophied, so that but little healthy secreting structure remains. In addition multilobular cirrhosis is met with not very rarely in chronic



PIVII. 5. — Dropsical type of Kala-azar produced by
enlargement of the liver.

kala-azar cases, and post mortem it is usually found to be associated with old chronic dysenteric lesions. Such cases are liable to be mistaken for so-called Banti's disease.

Advanced stages of this form of cirrhosis are accompanied by ascites and the usual symptoms of this affection of the liver. Plate 5, opposite page 36, illustrates the appearance in this type of kala-azar. It may run a slow course, but is generally ultimately fatal, although in one case shown me by Dr. Price recovery followed repeated tapping. The spleen is usually also greatly enlarged, an important point in distinguishing this cirrhosis from other forms, but it is generally very difficult to puncture the organ on account of its sinking back into the ascitic fluid the moment the needle touches it. The parasite may, however, sometimes be found by puncturing the liver itself. Repeated tapping is the only measure which is likely to ameliorate the condition, but this has rarely been followed by recovery.

THE BLOOD CHANGES IN KALA-AZAR

As the parasite of kala-azar is found much less frequently and with far greater difficulty in the peripheral blood than are those of malaria, any alterations in the composition of the blood which may be of diagnostic value are of the greatest practical importance, and these have been carefully studied in a large number of cases with the following results.

Degree of Anaemia.—Clinically marked anaemia is only a feature of the later stages of the disease, although the haemocytometer shows some decrease of the red corpuscles to be present in the great majority of the cases after the first month. Table IV. gives the data from 83 cases in the Calcutta European Hospital in which the counts were made, classed according to the duration of the disease at the time the blood was examined.

TABLE IV.

Red Corpuscles.	Under 1 Month.			1-6 Months.			Over 6 Months.			Total.	
		%		%		%		%			
+ 4,000,000	.	.	.	11	55	7	25·9	7	19·4	25	30·1
- 2,500,000	4,000,000	.	.	8	40	18	66·7	19	52·8	45	54·2
- 2,500,000	.	.	.	1	5	2	7·4	10	27·8	13	15·6

The table shows that the anaemia progressively increases with the duration of the disease, and it rarely reaches the advanced degree of under 2,500,000 red corpuscles per cubic millimetre in less than six months from the commencement of the fever. Further, in only 3 cases did the number fall below 2,000,000, the lowest count being 1,770,000 in a case of over a year's duration. High degrees of anaemia are usually of bad prognostic import, but 3 cases with counts between 2 and $2\frac{1}{2}$ million red corpuscles recovered. The moderate degrees of between $2\frac{1}{2}$ and 4 millions are most frequently met with, except during the first month of fever when the majority of the patients showed over 4 millions.

Blood counts in 100 cases of chronic splenomegaly with negative spleen punctures in Calcutta, and which were almost certainly mostly chronic malaria, gave closely parallel

red corpuscles counts to kala-azar, so these counts are of no diagnostic value. Very anaemic cases with less than 1,500,000 red corpuscles should not be submitted to spleen puncture for fear of haemorrhage.

The Haemoglobin and Colour Index.—The percentage of the haemoglobin in kala-azar falls in much the same proportion as the number of the red corpuscles, so that in fifty observations made in Assam the haemoglobin value, or colour index, averaged exactly the same as that of healthy natives of that province, namely 0·65—the normal figure for these vegetarian people being much lower than the European standard. In this respect the blood in kala-azar presents similar characters to that of malaria, the anaemia in both diseases being of the pernicious type. On the other hand, this feature served completely to differentiate kala-azar from ancylostomiasis, with which it had been reported to be identical in 1891, for in the latter the anaemia is so typically of the chlorotic type, the colour index rarely exceeding 0·4, that uncomplicated cases of the two diseases could be absolutely differentiated by this point alone, as shown in my 1897 report on kala-azar.

The Number of the White Corpuscles.—The changes in the leucocytes in kala-azar are much more characteristic and important than those of the red corpuscles. They are of two kinds, namely an alteration in the total number and a change in the proportions of the different varieties of the white corpuscles. In uncomplicated cases of the disease there is always a reduction in the total number of the leucocytes, which soon attains to a high degree. In Table V.A are given the counts obtained in 76 cases of the sporadic form of kala-azar mostly in natives examined in Calcutta Medical College Hospital, all verified by demonstrating the parasite in the spleen blood, and nearly all in a typical fairly advanced stage. In only four were over 3000 leucocytes per cubic millimetre found, and in three of these inflammatory complications, which might be expected to increase them, were present, while the fourth was a recovering case with very few small parasites in the spleen blood. In 22 per cent more from 2000 to 3000 were found, while in no less than 72 per cent the leucocytes numbered less than 2000, in the majority of which they were actually less than 1000 per cubic millimetre. Such low counts as these are rarely met with in other fevers, although they may occasionally fall to between 2000 and 3000 in true malarial cachexia.

The period of the disease when the marked leucopaenia occurs may be studied in Table V.B, showing 84 counts in sporadic kala-azar cases in the European General Hospital, where they sometimes come earlier under observation. Here it will be seen that during the first month of the disease the leucocytes may not infrequently be only slightly reduced in numbers, although even at this early period less than 2000 per cubic millimetre were found in one-half of the cases. Among the 10 cases showing over 3000, 4 were uncomplicated very early ones, but all but one of the remainder were suffering from some leucocyte-increasing inflammatory complication. In 62 per cent of the total less than 2000 leucocytes were present, even in this comparatively early series.

The Reduction in the White Corpuscles relatively to the Red.—As in true malarial cachexia there may sometimes be just as marked leucopaenia as in many cases of kala-azar, the total leucocyte count will not always suffice for the differentiation of these two

TABLE V.A.—LEUCOCYTE COUNTS IN SPORADIC KALA-AZAR VERIFIED BY SPLEEN PUNCTURE

	Died.	Worse.	Doubtful.	Improved.	Total.	Percentage.
PART I.—Total leucocyte count in 76 cases :—						
Over 6000	0	0·0
4000–6000	2	2	2·6
3000–4000	1	2	2·6
2000–3000	2	1	4	10	17	22·4
1000–2000	5	4	6	8	23	30·3
1000 and less	9	5	9	9	32	42·1
Total						
PART II.—Ratio of white to red corpuscles :—						
1 to 750	2	..	1	..	3	4·0
1·750 to 1·1000	1	..	2	4	7	9·2
1·1000 to 1·1500	1	1	7	4	13	17·1
1·1500 to 1·2000	4	3	1	6	14	18·4
1·2000 to 1·3000	2	2	5	3	12	15·8
1·3000 to 1·4000	3	1	4	7	15	19·7
Less than 1·4000	5	3	0	4	12	15·8
Total less than 1·1500	14	9	10	20	53	69·7
Grand total	18	19	20	28	76	
PART III.—Total polynuclear white corpuscles :—						
Over 3000	0	0·0
2000–3000	1	..	1	..	2	3·0
1000 to 2000	2	..	2	9	13	19·7
500 to 1000	5	4	5	8	22	33·3
250 to 500	4	4	6	7	21	31·7
Less than 250	5	1	1	1	8	12·4
Total	17	9	15	25	66	
PART IV.—Large mononuclear count in uncomplicated cases :—						
0 to 8 per cent	1	4	5	11·9
8 to 12 "	1	2	5	8	19·1
12 to 15 "	2	1	4	4	11	26·2
Over 15 "	2	6	2	8	18	42·8
Total	5	8	8	21	42	

clinically closely similar conditions. This very desirable end may, however, be commonly obtained by counting the number of the red corpuscles as well as the white, and working out the ratio between the two. Table V.A, Part II., shows the figures obtained in 76 cases verified by finding the parasites of kala-azar in the spleen blood. The normal ratio of about 1 white to 750 red corpuscles was only observed in 3 of the cases, while in 7 more it was between that figure and 1 to 1000, but no less than 8 of these 10 had some inflammatory complication to increase the leucocytes, such as dysentery, phthisis, cancrum oris or meningitis. The remaining 2 were recovering, having lost their fever, and showed very few parasites. In 13 more cases, or 17 per cent, the ratio was between 1 to 1000 and 1 to 1500, a slight relative reduction of the white corpuscles which occurs occasionally in typhoid and also in seven-day fever, but less frequently in malaria. The remaining 70 per cent of the cases showed less than 1 white to 1500 red, which is less than half the proper proportion, while in half the total cases the ratio was less than 1 to 2000 : a degree of relative reduction of the white corpuscles which I have not met with in any other fever which could be confused with kala-azar. If cases showing inflammatory complications are excluded, then the proportion of the uncomplicated kala-azar cases in which the ratio was less than 1 to 1500 rises to nearly 90 per cent, so that *this degree of relative leucopaenia is almost absolutely diagnostic of these typical stages of sporadic kala-azar*, and very similar figures were previously obtained in a number of the Assam Epidemic cases in 1897.

Here, again, it becomes of importance to ascertain how early in the disease this sign is present, and in Table V.B, Part II., of the European Hospital series the necessary data will be found. The most striking thing about this table is the very close similarity of the figures in this comparatively early series of cases to those just given for the later native hospital ones. Thus in only 10·8 per cent was the ratio of white to red corpuscles over 1 to 1000 ; in all but one of these cases there was some inflammatory complication, while the exceptional one had been free from fever for some time. In the intermediate degree of from 1 to 1000 to 1 to 1500 there was slightly a larger percentage of cases, namely, 21·7 per cent, nearly half of which were in patients who had suffered from fever for less than one month, so that this blood change is somewhat less marked in the very early stages of the disease. On the other hand, in no less than 67 per cent of even this series (including complicated cases) the ratio of white to red corpuscles was less than 1 to 1500, and in 50 per cent under 1 to 2000.

The time at which the count is made is not without importance, for in regard to the epidemic kala-azar I recorded some years ago that the leucopaenia is less marked during high fever than during remissions or low intermittent pyrexia. On examining the charts of the European series in which the intermediate degree of relative leucopaenia had been detected, namely, between 1 to 1000 and 1 to 1500, it was found that in nearly every uncomplicated case the blood had been taken during remittent pyrexia, except in a few exceedingly early cases not recognizable as kala-azar until a later date. It is therefore clear that if a doubtful degree of relative leucopaenia is found during remittent fever, a second count should be made when the remittent undulation is at an end, when a characteristic degree of this condition will probably be met with if the case is one of kala-azar. In the series of chronic splenomegaly, with negative spleen punctures, less than 1 white to 1500

TABLE V.B.—LEUCOCYTE COUNTS IN SPORADIC KALA-AZAR OF VARIOUS DURATION

	Month.	Months.	Months	Months.	Year			
PART I.—Total leucocyte counts :—								
Over 6000	1	2	2·4	
4000-6000	.	.	4	2	.	8	9·6	
3000-4000	.	.	2	.	3	7	8·4	
2000-3000	.	.	4	2	2	14	16·9	
1000-2000	.	.	8	5	11	31	37·4	
1000 and less	.	.	2	5	6	22	25·3	
Total	.	.	20	14	14	81		
PART II.—Ratio of white to red corpuscles :—								
1 to 750	.	.	1	.	2	4	8·4	
1-750 to 1-1000	.	.	1	1	.	2	2·4	
1-1000 to 1-1500	.	.	7	2	1	4	21·7	
1-1500 to 1-2000	.	.	6	.	3	2	16·9	
1-2000 to 1-3000	.	.	1	5	5	18	21·7	
Less than 1-3000	.	.	5	5	4	7	27·9	
Total less than 1-1500	.	12	10	12	17	56	66·6	
Grand Total	.	.	20	14	13	83		
PART III.—Total polynuclear white corpuscles :—								
Over 3000	.	.	1	1	.	2	4	5·2
2000 to 3000	.	.	3	1	1	2	7	9·2
1000 to 2000	.	.	8	2	3	3	19	25·0
500 to 1000	.	.	7	1	3	5	21	27·6
250 to 500	.	.	.	4	3	7	1	19·7
Less than 250	.	.	2	.	2	4	2	13·1
Total	.	.	21	12	12	19	12	76
PART IV.—Percentage of large mononuclear white corpuscles :—								
0 to 8 per cent	.	.	3	1	4	1	2	15·3
8 to 12	"	.	5	5	2	4	2	25·0
12 to 15	"	.	6	3	1	6	2	18
Over 15	"	.	6	1	5	8	4	25
								34·7

red corpuscles were found in only 18 per cent, while in none of these was the history of fever of less than one year's duration.

To sum up, it may be laid down that *in any case of fever which may possibly be kala-azar the finding of less than 1 white to every 1500 red corpuscles, and still more of greater degrees of relative leucopaenia, will be almost diagnostic of the disease.* This degree of the condition may, however, be absent in kala-azar firstly, during any inflammatory complication, such as pneumonia, dysentery, cancerum oris, meningitis, phthisis, etc. ; secondly, during high remittent pyrexia occasionally ; and thirdly, during the very earliest stages of the disease such as the first month of fever, or in recovering patients who have been free from fever for some time.

The Differential Leucocyte Count.—In addition to the decrease in the total number of the leucocytes in kala-azar, we also find a marked change in the proportions of the different kinds. Briefly, this consists in a considerable and not rarely an extreme reduction of the percentage of the polymorphonuclear neutrophiles (called by the simpler term polynuclears henceforward) and eosinophiles accompanied by a relative increase in the proportion of the large mononuclears and lymphocytes, although owing to the great total reduction these also are commonly below the normal number per cubic millimetre of the blood. Of these changes the increase of the large mononuclears is most important from the diagnostic point of view, and the decrease of the polynuclears from that of prognosis.

As the large mononuclear increase is common to both kala-azar and malarial cachexia its presence is of no value in differentiating these two similar diseases. On the other hand, it is of the utmost value in separating the high remittent fever of kala-azar in its difficult early stages from typhoid, under which heading such cases are almost always returned, for Table XXII. on page 131 shows that an increase of the large mononuclears in typhoid during fever is very rare.

As it is just in this early stage of kala-azar that the relative leucopaenia sometimes fails to differentiate the disease from typhoid, the presence of a large mononuclear increase in the former disease may be of great help in raising a suspicion that the disease is not typhoid, and may be kala-azar, and a negative Widal test after the tenth day of the disease will serve to strengthen such an opinion.

The Decrease of the Polynuclear Leucocytes is shown in Table V.A, Part III., which gives the total numbers per cubic millimetre of blood, calculated from the total and differential leucocyte counts in 66 cases verified by finding the parasite in the spleen blood. Bearing in mind that the normal number is about 5000, the great reduction in kala-azar is brought out by the fact that in no case were over 3000 found, while both of the cases in which between 2000 and 3000 were present had inflammatory complications. Thus no uncomplicated cases had as many as two-fifths of the normal number, in 77 per cent of them under 1000, or one-fifth, of the normal number of polynuclears were present in the blood, while in 40 per cent they were less than one-tenth of the proper total. In children the polynuclears several times did not number over 5 per cent of the total leucocytes, and in such less than one-hundredth of the normal total polynuclears were present. Moreover, the table shows that the prognosis becomes progressively worse as the polynuclears become fewer and fewer, so that this estimation is of definite prognostic value. The European Hospital cases in Table V.B, Part III., again show that this also is a

progressive change, being much less marked in the first month of the disease, and becoming much more often extreme after six months of fever.

This extraordinary polynuclear decrease is of great importance from another point of view. It will be shown a little farther on that a considerable majority of kala-azar patients actually die from some secondary inflammatory complication, especially those produced by coccal and bacterial invasions (see p. 44). *That the loss of nine-tenths or more of the phagocytic polynuclear leucocytes will strongly predispose to such terminal invasions will be evident.*

The great reduction in the polynuclear leucocytes is no doubt connected with the fact that when the parasites of kala-azar are found in the peripheral circulation, they are almost invariably situated in these corpuscles, and are pretty certainly carried in them to the spleen, liver and bone marrow, where they accumulate and multiply. The steady reduction in the polynuclears is thus readily explained, and when it reaches a high degree the very fatal terminal inflammatory infections are liable to ensue. As comparatively few cases die from the primary fever in spite of it frequently persisting for many months without some such secondary complication, this polynuclear decrease appears to be the most essential pathogenic change in bringing about a fatal termination in kala-azar. This view of the pathology of the disease is supported by the fact that when any great increase of the polynuclears is brought about by the reaction of the system to any secondary inflammatory complication, a temporary and not very rarely a permanent improvement in the case sets in, as in Case 6 (p. 28). On the other hand, if no such increased polynuclear reaction occurs during such inflammatory complications as cancrum oris, etc., then the prognosis is exceedingly bad and death usually rapidly ensues. Injections of staphylococcus vaccine have several times been followed by a considerable increase of the polynuclear corpuscles and great improvement and even recovery of the patient.

The Lymphocytes are increased together with the large mononuclears in proportion to the reduction in the percentage of the polynuclears and eosinophiles. As such an increase also occurs in both true malarial cachexia and in typhoid this change is of little diagnostic value.

The Eosinophiles are decreased, in the absence of intestinal parasites, so that in a count of 250 to 500 leucocytes as a rule no eosinophiles will be met with. This change is apparently similar in nature to the loss of the polynuclears, but is less significant owing to the small numbers of these corpuscles normally present in the blood.

The Coagulability of the Blood.—The frequency with which haemorrhages of various kinds complicate kala-azar is pointed out on p. 45. In such cases the coagulability of the blood is decreased, the time taken for the blood to clot in Wright's tube being longer than the normal lower limit of five minutes. This change is most marked in anaemic cases. In patients who are very anaemic, or have suffered from haemorrhages, spleen puncture is dangerous and should not be done unless the blood has first been proved to be clotting within the normal time limit. Estimations of the coagulability by Wright's method

in a series of verified kala-azar cases, however, showed the time to be only occasionally increased to over five minutes.

The Alkalinity of the Blood was first found to be reduced in 4 cases by Archibald in the Sudan, and independently in a number of cases in Calcutta by Shorten and myself. I tried intravenous injections of sodium bicarbonate, which were several times followed by a rapid fall of temperature, but unfortunately the improvement was only of a temporary nature.

Complications.—The frequency with which kala-azar is terminated by some inflammatory complication has already been mentioned, and is well illustrated by 40 post-mortems on natives made by me at the Medical College Hospital, Calcutta. All but 7 showed some serious local disease, and some of them more than one. In 11 pneumonia, in 10 dysentery, in 7 cancerum oris, in 2 each pneumonococcus meningitis, purpura, cerebral haemorrhage, and phthisis respectively were found, and in 1 pericarditis. In several of the cancerum oris cases staphylococci or streptococci were cultivated from the spleen, thus revealing a general septic infection. The extreme reduction of the polynuclear leucocytes in kala-azar, in which they frequently fall to from one-twentieth to one-hundredth of their normal numbers, easily explains the frequency with which these patients fall victims to the specific organisms of pneumonia, dysentery, phthisis or the cocci of septic infections, including cancerum oris, in which I have never been able to find the diphtheria bacillus, which has been met with in European cases of this disease.

Among 111 cases of sporadic kala-azar, including 37 children and twice as many adults, in the European Hospital the complications shown in Table VI. were met with.

TABLE VI.—THE COMPLICATIONS OF KALA-AZAR

	In Children up to 15.	In Adults	Total	Died	Percentage,
Cancerum oris	11	9	19	11	17.2
Other septic conditions	2	2	4	2	3.6
Pneumonia	2	7	9	5	8.1
Phthisis	1	2	3	1	2.7
Dysentery	4	1	5	2	3.6
Haemorrhages	1	5	6	5	5.4
Total	22	26	46	26	41.4

In addition pleurisy, dropsy, cystitis and tenderness of the testicle occurred in one case each.

Cancerum Oris and other Septic Conditions are the most frequent and important complications. The latter include mastoid abscess, otitis media, sloughing of the scrotum and extensive ulceration following an eruption of herpes zoster. The remarkable frequency of these conditions in children, over one-third of whom showed them while in hospital, is of interest in connexion with the fact that the reduction of the total polynuclear white

corpuscles is commonly more extreme in them than in adults, *under 100 per cubic millimetre*, or less than one-fiftieth of the normal numbers having repeatedly been found in children in the advanced stages of kala-azar. Moreover, I have occasionally found a reduced opsonic index to staphylococci shortly before an attack of cancrum oris. Since injections of staphylococcus vaccine have been used to increase the number of white corpuscles, cases of cancrum oris in children so treated have become distinctly fewer, while at least temporary improvement of an actual cancrum oris has also been observed after such injections, but more work is required in this direction before the precise value of this treatment can be decided.

Chart 6 illustrates the extraordinary recovery which sometimes takes place after an attack of cancrum oris, when a considerable increase of more especially the polymorphonuclear leucocytes follows the septic complication; several other similar permanent cures led me to adopt the vaccine treatment with some success, although it is now superseded by antimony preparations. In adults an autogenous staphylococcus vaccine has repeatedly in my hands been successful in checking the spread of the sloughing process, and several such cases have ultimately completely recovered from kala-azar, although sometimes the sear tissue greatly limited the power of opening the mouth. This should be guarded against by stretching measures. In children vaccines usually fail to control cancrum oris, which is very deadly in them.

Pneumonia is the next most frequent and fatal complication in kala-azar, and here again permanent cures occasionally follow recovery from the disease in early cases, if a marked increase of the polymorphonuclear leucocytes ensues. Unfortunately, however, this complication is an exceptionally fatal one. It differs from ordinary forms of pneumonia by the usual absence of a marked leucocytosis, the greatly reduced number being only slightly increased up to from 3000 to 6000 as a rule—a peculiarity which distinguishes acute inflammation of the lungs in kala-azar from other forms. The pneumococcus is most commonly present in the disease.

Dysentery is less common in European patients than in natives, and also gives rise to at least a temporary increase of the leucocytes, and especially of the polymorphonuclears, which, according to Patton, may frequently contain the parasites of kala-azar in the peripheral circulation. It is usually of the bacillary type, Shiga's bacillus having been cultivated post mortem by me in several cases. If of the amoebic type, the accompanying increase of the leucocytes may have a beneficial effect for a time.

Phthisis is usually a late complication in chronic cases. This leads to some increase of the leucocytes, and in one case recovery from both diseases occurred.

Haemorrhages form a common and very fatal complication, and may occur in various parts of the body. In several cases a meningeal haemorrhage has terminated the disease, both in the epidemic and sporadic forms. I have seen fatal haemorrhage from the bowel, and post mortem in another case the stomach showed extensive sub-peritoneal extravasation. Cancrum oris may also end in uncontrollable loss of blood. More frequent than these are purpuric haemorrhages in the skin, most commonly on the legs, but often on the trunk as well. They are accompanied by a reduction in the coagulability of the

blood, and are of very bad prognostic import ; five of the six cases in which haemorrhages occurred died in hospital, the remaining one was discharged in a very bad condition and was lost sight of. In fact I know of no case which recovered after well-marked purpura had appeared.

Mortality.—The mortality of the Assam epidemic of kala-azar was 96 per cent on tea-gardens, where reliable figures could be obtained in several hundred cases of Dodds Price's. In Madras the death-rate was also well over 90 per cent, some doubting if recoveries took place. In the more chronic type in Bengal recoveries are certainly not very rare, but as the duration of the disease may be anything from two to ten years, it is very difficult to fix accurately the mortality, but in cases I have been able to follow up it was not less than 75 per cent under careful treatment before the value of antimony was discovered, and probably still higher. In China, Cochran records that every case died, but, in the Sudan, Thomson and Marshall saw a few recoveries. Under the present specific treatment with soluble antimony salts intravenously, only very advanced and complicated cases are lost and the mortality in European patients has been reduced in Calcutta to practically nil.

In infantile or Mediterranean kala-azar the mortality used also to be very high, and has been greatly reduced by the same treatment, although not quite to the same extent owing to the difficulties of intravenous injections in young children.

DIFFERENTIAL DIAGNOSIS OF KALA-AZAR

On account of the great difficulties of the subject it may be well to recapitulate the most important points in the distinction of kala-azar from other fevers met with in the tropics, treating separately the characteristic advanced and the less marked early stages.

Diagnosis of the Typical Advanced Stage from Chronic Malaria.—This presents little difficulty at the present time if the patient is under observation for some days, although at a single clinical examination it may be impossible to distinguish between kala-azar and a true malarial cachexia. The effect of quinine will soon decide the point, for in a malarial case it will stop the fever within 2 to 7 days, and prevent recurrences as long as it is persisted with. In kala-azar the drug may lower the temperature curve, especially if it presents the remittent type ; but low intermittent fever will continue for a long time in spite of large doses of the drug. Moreover, a four-hourly chart in kala-azar will not present the typical paroxysms of malarial fevers described on pp. 242-246, but it more commonly shows a low continued or an intermittent rise to only about 100 ; this does not occur for any length of time in malaria. The double remittent diurnal rise of temperature, so characteristic of kala-azar, may also appear at any time in the course of the disease, but most commonly occurs during remittent exacerbations of the fever.

On examining the blood, when no quinine has been taken for several days, malarial parasites will be absent in uncomplicated kala-azar, but will usually be readily found in chronic malaria. The differential leucocyte count shows the same changes in both diseases, but the ratio of the white to the red corpuscles will generally allow of their being readily

distinguished ; for in malaria they are reduced in about equal proportions, while in uncomplicated kala-azar the white are reduced at least twice as much as the red, so that the proportion of white to red is less than 1 to 1500, and commonly much lower. The most extreme degrees of leucopaenia are practically diagnostic of kala-azar as against any other tropical fever. In acute types the parasites may frequently be found in advanced cases by prolonged search in the peripheral blood, especially if complicated by dysentery or other leucocyte-increasing disease.

By attention to the above points the typical stages of kala-azar can readily be recognized, and spleen puncture, which may be dangerous in these advanced cases, is very rarely required to establish the diagnosis.

Malta fever, fortunately, is not known to occur in those parts of India where kala-azar prevails, as in chronic cases the temperature curve may somewhat resemble that of kala-azar. The spleen and liver in Malta fever, however, very rarely present the great enlargement of the protozoal disease, while the leucocytes are not decreased in numbers, but tend to be slightly increased. The serum test will further distinguish any doubtful cases.

Relapsing fever also mostly occurs in parts of India which are free from kala-azar, but clinically the two can hardly be confused, and a glance at a stained blood film will allow the distinguishing leucocytosis of relapsing fever to be recognized, while the spirillum can be found in blood films during fever.

The Early Stages of Kala-azar.—The early diagnosis presents great difficulties. It was only by examining every fever case in the Calcutta European Hospital for two years and following them up that I was able to obtain the necessary material for the description of the early stages of the disease. The remittent pyrexia of early kala-azar has nearly always been mistaken for either typhoid, or "remittent malaria." The latter disease can be readily excluded by the quinine test.

The differentiation from **typhoid** and **para-typhoid** is a much more difficult matter. *The high continued type of fever, especially with a slow pulse, is almost conclusive evidence of typhoid as against early kala-azar, while the high remittent type is almost equally rare in the latter disease.* Some typhoids, however, show the low remittent type which is common in kala-azar, and if a negative serum test has also been obtained, the blood changes must be turned to for help. Especially frequent in these early stages is the double remittent type of pyrexia I have described, for although I have never seen it in typhoid or malaria, its occurrence is almost, if not quite, diagnostic of kala-azar : the first case recognized in a European in Bombay by L. F. Childe, I.M.S., was first suspected on account of the appearance of this sign. The absence of severe constitutional disturbance and of abdominal or respiratory symptoms with a persistent remittent fever, also points to kala-azar as against typhoid. Moreover, the spleen is commonly enlarged down to the navel quite early in the pyrexia of kala-azar, but not in any other tropical fever that I know of : a point of great diagnostic value.

In addition to the above clinical features, we derive most valuable assistance from the blood changes. The most important of these is undoubtedly the great relative reduction of the white corpuscles, which has been met with in an extreme degree in some very early cases, even before the spleen had become at all enlarged, and alone led me to a correct

diagnosis. In addition there is commonly a marked increase in the percentage of the large mononuclears, which rarely occurs in the early stages of typhoid, and so may be considered as an important point in favour of early kala-azar. In the more acute types seen in Assam and Madras the presence of the parasites in the peripheral blood may also be of great diagnostic value.

The above points will usually allow of a diagnosis of kala-azar being made before the advanced condition has been reached. When any doubt remains spleen puncture may be performed, as with the precautions laid down below it is a safe procedure, especially in early cases, while now that we have a specific curative treatment it is most important to be certain of the diagnosis to enable the requisite antimony injections to be commenced as early as possible. Early treatment affords every prospect of saving the patient's life.

Spleen Puncture as a Diagnostic Measure.—This method should not be used (1) in very advanced cases, and especially in those showing great anaemia, such as less than 1,500,000 red corpuscles; (2) in patients showing a coagulability time of over five minutes with Wright's tubes, a test being always made before the operation is undertaken; (3) in any cases showing any haemorrhagic condition, such as purpura, and (4) in all those with any trace of ascites. In such advanced cases the diagnosis is nearly always easy, especially if a blood count is done. This will commonly reveal a great leucopaenia, and spleen puncture in consequence be unnecessary.

In carrying out the operation the skin over the organ is first sterilized. A small 2 or 3 c.c. hypodermic syringe, with a fine but strong needle about 2 in. in length, is plunged deeply into the enlarged organ through the abdominal wall, preferably in the right linea semilunaris, if the organ is much enlarged. The piston, which must be tightly fitting, so as to have considerable suction power, is now gradually withdrawn, and if a few drops of blood slowly enter, this blood will be sure to contain spleen pulp and be satisfactory for examining. If, however, the blood enters the syringe very rapidly a vein must have been entered, and the blood will contain few if any parasites. In that case it is well to withdraw the needle partly, pass it in another direction, and again apply suction. As the needle is finally taken out, a piece of cotton-wool soaked in carbolic or other antiseptic is firmly applied over the puncture, and digital pressure should be kept up for several minutes, a dose of 30 grains of calcium chloride in an ounce or two of water being administered at once, so as to increase the clotting power of the blood, and a pad and a bandage applied tightly and left in position for twenty-four hours. Muir advises keeping up digital pressure for half an hour after the puncture, and states that in many scores of operations he has never lost a case in which proper precautions were carried out. If the blood has run very readily into the syringe the pressure should be kept up for at least 10 minutes, by which time the calcium salt will have had time to act. The patient should be kept lying in bed for 24 hours after the operation. With the preliminary testing of the coagulability and the above precautions, spleen puncture can be safely performed, although it should never be looked on as other than a serious undertaking.

Some writers have recommended puncturing the liver in preference to the spleen as being less dangerous, but I have heard of a fatality after liver puncture in kala-azar. The

organisms of kala-azar can certainly be found in the liver blood, although slightly less readily than in that of the spleen, and, where the former organ was much enlarged and the spleen only slightly so, I have punctured the liver successfully in preference. In other conditions the spleen blood is the more likely to furnish organisms on culture. It is in early, doubtful cases that spleen puncture furnishes the most valuable information, and it is then also least dangerous.

Is there a Common Form of Chronic Splenomegaly in Tropical and Sub-tropical Countries distinct from Kala-azar and Chronic Malaria?—This question presents the most difficult problem in the differential diagnosis of the very chronic forms of kala-azar met with in Lower Bengal more especially. Nor is the problem peculiar to India, for Day and Fergerson have described a form of splenomegaly often complicated by hepatic cirrhosis of the portal type in Egypt; Nicolle and others have recorded doubtful cases resembling closely infantile kala-azar in Tunis and other Mediterranean countries, and Wooley has raised the same question in the Philippines. For several years I studied this problem closely in Calcutta during work on the treatment of kala-azar, keeping careful notes of those cases in which spleen puncture revealed no Leishman-Donovan parasites as well as of the positive cases, and analysing each series of records with the following main results. Out of 166 consecutive cases admitted to my kala-azar beds as possible cases of that disease, in only 66, or 40 per cent, were the Leishman-Donovan parasites found by spleen puncture, but all except one of the positive cases had fever of a persistent nature, never yielding within a week to ordinary doses of quinine, which was given in a large number of them to test this point. Of 114 cases showing fever while in hospital the parasites were found in 57 per cent. The size of the spleen and liver, the degree of anaemia or the seasonal incidence of the admissions afforded no help in distinguishing between the kala-azar and other cases of splenomegaly, but great leucopaenia, such as less than 1 white to 1500 red corpuscles, was greatly in favour of kala-azar and practically diagnostic of that disease if the fever had persisted for less than one year. Great loss of weight, especially if it persisted in hospital, was much in favour of kala-azar.

On turning to the negative cases the most striking fact is that 51 per cent of the patients had no fever at all during their stay in hospital, usually in these cases only for a week or ten days; while in 31 per cent more the fever soon fell to normal in all except two within a week of admission, usually under quinine treatment, and in no single case did the fever persist for more than a week while taking quinine, although in the kala-azar cases the shortest duration of the fever in hospital was fifteen and twenty-seven days in one case each, and in the others from one to two and a half months. It should be mentioned that a large number of these cases occurred before the tartar emetic treatment was commenced. In a few of the negative cases malarial parasites were found, but unfortunately I had not time to examine most of them carefully for these organisms. In only 7 of the remaining cases did fever persist for over a week under quinine treatment, and some of these may have been kala-azar, as I know from experience that not very rarely the parasites are found on a second spleen puncture after a previous negative one. In 17 negative cases in which quinine was not given the fever lasted over a week, and in 13 of them there was a previous history of malaria-like attacks. The great majority of the non-kala-azar cases

of splenomegaly came from highly malarious districts of Lower Bengal. The practical conclusion I came to was that the temperature curve and reaction to quinine afford great diagnostic aid, for fever with splenomegaly in Bengal in which fever persists for over a week under 20 to 30 grains of quinine a day is almost certainly kala-azar, and should be treated as such—a point of great value in a country where few of the medical practitioners have the necessary time and skill for doing spleen punctures and microscopical examinations.

The question remains as to the nature of the non-kala-azar cases of splenomegaly. In the first place there can be little doubt that most of the febrile ones yielding rapidly to quinine are malarial. Of the considerable number of afebrile cases, a large proportion must be also malarial admitted during an apyrexial period, for I found that quinine and arsenic rapidly diminished their spleens. Some must be recovering kala-azar cases, for I have long been of the opinion that in the very chronic Lower Bengal type of kala-azar spontaneous recoveries are by no means as rare as many think. Moreover, it has been abundantly proved that the percentage of enlarged spleens in children at any rate is a good test of the malariousness of any district or place. Personally I came to the conclusion that malaria and kala-azar sufficiently account for all the cases, and a most careful analysis failed to reveal any new forms of disease, although I readily admit that it is quite possible that such exist. It is of interest to note in this connexion that the so-called Banti's disease has been mainly met with in areas in which infantile kala-azar exists. It has been shown also to affect adults, while in at least one museum specimen of a spleen removed for Banti's disease abundant kala-azar parasites were subsequently found.

TREATMENT

As early as 1897 I drew attention to the remarkable occasional spontaneous recoveries from kala-azar, even after the disease had reached a very advanced stage, which held out hope of a specific treatment being eventually found. I also became convinced that quinine, although it completely fails to stop the fever, still has some useful controlling influence on its course, if large doses can be tolerated, as in the recovering child whose temperature is recorded in Chart 7. Dodds Price treated 500 cases with quinine on my plan with a mortality of 75 per cent against a previous one of over 90 per cent, which still left much room for further improvement. I also pointed out that most of the spontaneous recoveries followed some leucocyte-increasing infection, such as cancrum oris and other septic diseases and pneumonia, although these complications are usually fatal in debilitated kala-azar subjects. I further found that such recoveries only occurred if a considerable increase of the leucocytes resulted from the complication, while in its absence such infections always proved fatal, and I have further shown that the gravity of the prognosis is in proportion to the degree of leucopaenia present, and have therefore advocated the use of leucocyte-increasing treatment, such as staphylococcus and other vaccines. Local irritation such as setons have been used, and Muir obtained improved results by the subcutaneous injections of turpentine for the same purpose. In a series of 27 cases treated with dead staphylococcus vaccines the following results were obtained. Cured, 0 (it was

not possible to follow them up long enough to see any cures); greatly improved, 14 (with a good prospect of recovery in at least 2); slightly improved, 6; unchanged, 3; and died, 1. These results were better than I had previously obtained with any drug treatment. I then tried living sensitized staphylococcus vaccines subcutaneously and intravenously, in the hope of producing a mild, but curative, infection, but although no harm was done, the results were not as satisfactory as with the simpler dead cultures. Vaccines made from cultures of the *L. donovani* have been made by Row in Bombay, but I failed to get any good results from them, while others have used them unsuccessfully in the Mediterranean form of kala-azar.

The close relationship between the chronic course run by African trypanosomiasis and Indian kala-azar and between the protozoal parasites which cause them, made the experimental work done on trypanosome infections in animals of great interest to investigators of kala-azar, and has led to a trial in the latter disease of most of the drugs which gave any promise of success against trypanosomes. Thus atoxyl, salvarsan, neosalvarsan, arseno-phenylglycin, hectine, ganyl, etc., have all been tried in kala-azar, especially in the Mediterranean form, but without any definite success when due allowance has been made for the occurrence of spontaneous recoveries.

It was not until attention was directed to antimony preparations that a specific treatment was discovered. As related in the section on the treatment of trypanosomiasis, Plimner and Thomson first showed the powerful toxic effect of sodium antimonial tartrate on trypanosomes in the blood of animals in 1907, and in the following year Broden and Rodhain got over the great difficulty caused by the extremely irritant effect on the tissues of this salt and of tartar emetic by giving the latter intravenously, and Kerendal subsequently cured himself of trypanosomiasis by this method of treatment. A further advance was made when in 1913 Viana and Machado in Brazil reported the cure of the South American form of cutaneous and mucous leishmaniasis with tartar emetic intravenously. This led several workers to try the drug in both the Mediterranean and Indian forms of kala-azar. To Di Cristina and Caronia of Palermo, Sicily, belongs the credit for being the first to record the successful use of tartar emetic intravenously in Mediterranean kala-azar in February 1915, and the credit is all the greater owing to the technical difficulties in so treating young children. They reported on 8 cases, of which 5 were cured, 2 recovering, and only 1 had died of nephritis. In the autumn of 1914 I made up sterile solutions of tartar emetic in capsules for trying this treatment in Indian kala-azar, but lost several months owing to having no hospital beds. Thanks to the kindness of my medical colleagues in Calcutta, early in 1915 I was able to commence the treatment, and had already obtained favourable results in a series of cases when the report of the Italian doctors' prior success reached me in India. Isolated cases of the use of antimony salts, usually in combination with other drugs, were recorded about the same time.

Tartar Emetic intravenously has undoubtedly proved a specific curative treatment of kala-azar, as will be seen from the following results. In the infantile form confirmation has been supplied by Spagnolio, who recorded 4 successful cases in 1916, while Longo in the following year, reporting on 43 cases, recorded that "the results were not very satisfactory, owing to irregularity in attendance, and, in some cases, unwillingness of

the parents to allow the treatment to be continued." He reports four deaths which seemed to be directly due to the tartar emetic, and advises that for out-patients the doses should be limited to from 1 to 4 centigrammes every three or four days. In the Indian form the author has reported several series of cases, those treated in the European General Hospital, with the kind help of N. H. Hume, being the most important, as they could be followed up much longer than the Indian cases in the Medical College Hospital. The results in the 35 European cases of which the records have now been brought up to a later date, show the following results :

Cured.	Greatly Improved.	Improved.	Died.
29	2	3	1 (phthisis).

By cured is meant that the patient had lost his fever for several months and regained his weight, while the spleen had usually receded beneath the ribs. Most of these patients have been seen or heard from up to from one to three years after leaving hospital, and remain in good health and are working, so they may be regarded as permanent recoveries. The five patients recorded as much improved or improved left hospital against advice before they had been sufficiently long under treatment for complete recovery to take place, some having remained less than a month. The only death was from phthisis in a patient who had recovered from his kala-azar as shown by a negative spleen puncture and the disappearance of his spleen beneath the ribs. Thus in no case had the treatment completely failed. The series includes six children, with five cures and one taken away greatly improved and not seen since. Subsequently to the series above recorded a number of further cases have been treated with equally good results with the exception of certain deaths from accidental toxæmia as recorded below. In Indian patients the results have been very similar except that in the more advanced cases seen among them several deaths have taken place from complicating pneumonia, dysentery or cancrum oris. In all my cases except the children positive spleen punctures were made. Muir at Kalno in the Burdwan district of Lower Bengal has also recorded very favourable results in a large number of cases. In his first series he used turpentine injections as well, and believes that they hastened the cures. In his second paper he reported favourable results in about 100 cases mostly confirmed by spleen puncture, and advises in addition oral administration once, or if well borne, twice, a day of Antimon. Tartar. gr. i., Acid. Tannic. grs. iii., and Sod. Bi carb. grs. iv. In 1917 he recorded an experience of 143 in-patient cases with 97 discharged cured after fever had been absent at least two months. Of the remaining 46 patients, 33 left hospital and 13 died, the latter being all in the last stages of the disease. These results are very good for the class of Indian cases coming to hospital. Christopherson in the Sudan also lost two of three very advanced cases.

Dosage and Toxicity of Tartar Emetic.—The doses of tartar emetic required for destroying the parasites within the human body approach rather closely to the toxic dose for man, and in addition to the deaths which have occurred after the use of the drug in very advanced and debilitated patients, others have taken place owing to the dosage being too rapidly pushed, as in two I have reported, while others have come to my knowledge. As the result of a careful study of the records of over 1000 intravenous injections

of tartar emetic in kala-azar I have formulated the following rules for the dosage in accordance with the weight of the patients, which ensures smaller doses being given to advanced emaciated subjects. Either a 1 or a 2 per cent solution may be used, and I prefer the latter as it enables a 10 c.c. syringe to be used for the maximum dose of 20 centigrammes, with a limit of 2 centigrammes for every 10 lb. body weight, while by injecting slowly into the vein it is at once greatly diluted. This maximum dose, however, should only be reached very gradually, and to commence with not more than 3 or 4 c.c., or 1 centigramme per 10 lb. of body weight should be given, and that only if the patient is in fairly good general condition, while in debilitated subjects not more than one-third of the maximum dose should be commenced with, and increased by $\frac{1}{2}$ c.c. at a time as long as no toxic symptoms are produced. In debilitated young children weighing only about 30 to 40 lb. not more than 1 centigramme is given at first, and increased by $\frac{1}{2}$ c.c. of a 1 per cent solution at a time up to a maximum of 3 c.c. As long as the solutions are freshly prepared and quite clear, showing no sign of fungus, growth or precipitation, I have found these doses quite safe. Coughing often occurs just after the injection, but is not of any importance. If, however, nausea, and still more if actual sickness occurs, this is a sign for decreasing the dose by $\frac{1}{2}$ c.c. until it does not recur. The earlier doses may be given every other day if well borne, but when the larger doses are reached once in three days is usually sufficient. A **temperature reaction** commonly follows the injection, being probably due to toxins set free by destruction of the parasites, and such reactions continue for some time after the temperature has fallen to normal on the days injections are not given. The cessation of reactions after full doses is a favourable sign as it indicates that few parasites remain in the system, but I agree with Muir in advising the injections to be continued for at least two months after the fever has ceased. Rapid gain in weight is also favourable, and this feature is often a very remarkable effect of the treatment, as in two European patients of mine who gained respectively 27 lb. in 37 days and 23 $\frac{1}{2}$ lb. in 27 days, both making permanent recoveries. They were seen over two years later in full work. The diminution in the size of the spleen often takes a considerable time, but in a number of my European patients it had receded beneath the ribs before they left hospital, although in many of them it reached below the navel on admission. As long as the spleen remains much enlarged I think there is a danger of a relapse occurring. An Indian patient I saw repeatedly in consultation, who went away for a change after she had been free from fever for nearly two months, and had gained several pounds in weight, returned after several months nearly as bad as before, and now full doses of tartar emetic appeared to have little effect on the fever, and I suspect the parasites had become antimony fast. Such cases emphasize the importance of continuing the treatment long enough to cure the patient completely.

In addition to the danger of increasing the doses of tartar emetic too quickly, I have also recorded two accidents due to solutions being used, contrary to my directions, after precipitation had occurred in them. Very severe reactions rapidly occurred, and a feeble child in an advanced stage of the disease died in the first instance, and two adult patients in the other with temperatures of 105° and 106° F. and collapse. Three patients who recovered after very critical reactions all had no further fever, and rapidly recovered completely, indicating that the reactions were accompanied by destruction of large numbers

of parasites. Chemical analyses of the solutions failed to detect the nature of the chemical change which had evidently taken place in the solutions. Muir has noticed that certain light samples of tartar emetic provoked reactions out of proportion to their curative action, and he has recently informed me that a solution in which slight precipitation had occurred gave severe reactions even after it had been filtered. In the fatal cases noted above the same doses from the same flasks had been used in the cases with benefit for several weeks before the accident occurred, so that some toxic change must have taken place in the solutions, and this danger requires to be borne in mind.

Sodium Antimonyl Tartrate, which was first used by Plimmer and Thomson in trypanosome infected animals, has also been given successfully in kala-azar by the intravenous method. H. Ghosh and U. N. Brahmachari have used it in a few cases in Calcutta. In view of the toxicity and occasional dangerous decomposition of tartar emetic, I have tried the sodium salt in a series of Indian cases under the same conditions and dosage as another series with tartar emetic, as animal experiments had convinced me that the sodium salt is slightly less toxic than the potassium one. In 11 consecutive, unselected cases, treated with sodium antimonyl tartrate, 9 had been discharged cured, and 2 severe cases, complicated respectively with dysentery and cancrum oris and with bronchopneumonia, had much improved at the time of reporting, and subsequently the latter 2 were also discharged cured. On comparing this series with 13 consecutive cases previously treated with tartar emetic in the same ward it appeared that under the sodium salt the average time before the fever stopped, apart from reactions due to the injections, was 21·2 days, and the quantity of the drug used was 54 centigrammes, against 26·2 days and 103 centigrammes in the tartar emetic series. Clinically the sodium salt caused less toxic symptoms and appeared to be distinctly the more satisfactory drug, and I now always use it in preference to tartar emetic, but in similar doses, only it can be given every other day with advantage.

Among other antimony preparations which have been used in kala-azar finely divided metallic antimony has been given intravenously, as first used in trypanosomiasis by Ranken in the Sudan, and by Brahmachari, who found it required fewer injections than tartar emetic in a few cases he tried it in. The same writer has tested a number of other preparations, as recorded in his small book on his investigations, but in too few cases, and for too short a time to allow of any opinion being formed as to their value. Of more importance is Caronia's trial in infantile kala-azar of intramuscular injections of acetyl-paminophenyl, stibiate of sodium supplied by the firm of Heyden, in doses of from 3 to 10 centigrammes in children under two years, and 5 to 15 centigrammes in older children, given every other day in each buttock alternately. Caronia has recorded three out of four successes with this remedy, and Khalina-Mariucci two recoveries. Owing to the technical difficulties in giving intravenous injections in children, and also in India by the less well-qualified Indian practitioners, it is very desirable that an efficient subcutaneous or intramuscular method should be available, which the above-named chemical may possibly supply. Further work is required in this direction.

The Technique of Intravenous Injections of Tartar Emetic and Sodium Antimonyl Tartrate Solutions.—If a few drops of tartar emetic escape around a vein acute pain and

inflammatory swelling, usually followed by a sterile abscess and thrombosis of the vein, result, which greatly retard the treatment. The sodium salt is distinctly less irritating, but still causes a good deal of pain and inflammation if it escapes into the tissues. To avoid this untoward result great care is necessary in fully distending the vein and using a fine sharp needle, and drawing up a little blood into the syringe to make sure the needle is in the vein before injecting very slowly the irritating fluid. I use a stout piece of rubber tubing tightly stretched round the arm and then one end passed in a loop under the other so as to be quickly pulled out, or the two ends may be clamped together with a forceps. If this plan is not successful in distending a vein the air-bag of a blood-pressure estimating instrument is very convenient for the purpose. The pressure is of course released before the injection is made.

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II. TRYPANOSOMIASIS, SLEEPING SICKNESS AND AMERICAN TRYPANOSOMIASIS OR CHAGAS' DISEASE

HISTORY

ALTHOUGH sleeping sickness has been known for over a century, it is only within the last few decades that a chronic form of fever in West Africa was found to be caused by a human trypanosome in the blood, which is now known to be identical with that discovered soon after in the cerebro-spinal fluid in sleeping sickness, thus proved to be but a late complication or extension of trypanosomiasis.

The earliest account of sleeping sickness is that of Dr. Winterbottom in 1803, who studied the disease in negroes at Sierra Leone. He describes the lethargic condition, the fatal course within three or four months, and the glandular enlargement in the neck, which he states was looked upon by the slave-dealers as indicating a disposition to the disease, on which account they would not buy slaves showing this symptom. In 1869 Dr. A. P. A. Guerin wrote on the disease as seen in Africans from the Congo district only, who had immigrated fairly recently to the West Indies, but not among those who had been living there for many years. A. Corre further described the disease in 1876 in Senegambia, while occasional cases were either brought to England for study or developed the disease there some time, as long as several years in certain instances, after having resided in West Africa.

Up to the end of the nineteenth century sleeping sickness was only known to occur in West Africa, from Senegal in the north down to the Congo Free State in the south, and extending inland to the Upper Niger and to the Stanley Falls on the Congo. The disease was mainly sporadic in its distribution, but villages were said occasionally to be depopulated by its ravages. With the opening up of caravan routes across Africa the disease began to spread more widely, and in 1900 it appeared in an epidemic form on the north shore of the great Victoria Nyanza lake in Uganda, and in the following year cases were admitted to the missionary hospital at Mengo under Drs. A. B. and J. H. Cook.

The disease increased so rapidly that at the end of 1901 Dr. A. Hodges estimated that in the Busoga district alone 20,000 persons had died, and in 1902 the Royal Society sent out a Commission to investigate the disease, the work of which has been continued by a succession of observers up to 1915. Before dealing with the researches on sleeping sickness in Uganda the discovery of human trypanosomiasis in West Africa must be related.

The occurrence of **Trypanosomiasis in West Africa** was first ascertained by Forde finding some peculiar active worm-like parasites in the blood of a chronic fever case at Bathurst in May 1901, which were recognized as trypanosomes by the late J. E. Dutton, who had been asked by Forde to examine them. The blood of this patient had previously been repeatedly examined by skilled observers with negative results, the organism not being constantly present in the disease, and often only in very small numbers, so as to be readily overlooked. Nepveu appears to have seen the same organism in Algeria in 1888. In 1902 Dutton and Todd recorded the results of an expedition to Senegambia to study human trypanosomiasis. As this parasite may be present in the blood with few if any symptoms of illness being present, they examined the blood of 1043 natives, mostly healthy children, who do not suffer quite so much from the disease as adults, and found the trypanosome in the blood of 6 of them. The patients presented no constant characteristic, the symptoms consisting of very mild intermittent fever, with slight loss of strength, or there was an entire absence of symptoms, so that it was impossible to diagnose the affection clinically. The importance of the discovery consists in the fact that the apparently mild disease produced by the blood infection with trypanosomes is liable at any time to pass on into the exceedingly fatal sleeping sickness, brought about by the passage of the organism into the cerebro-spinal fluid, although it is not yet quite certain that this complication necessarily ensues in every case. That death is the usual fate of these victims is shown by the fact that out of 13 patients in whose blood trypanosomes were found by Colonel Bruce and his coadjutors in June 1903, and who were followed up by successive members of the Royal Society's Commission, only 1 was alive in April 1906, and he was beginning to show signs of sleeping sickness. Ten of the others had died of that disease and the remaining 2 of pneumonia. It is clear from this that the vast majority of patients suffering from the apparently mild trypanosomiasis sooner or later develop the deadly sleeping sickness if left to their fate. Fortunately recent experimental work indicates that by prolonged treatment the extension of the disease to the cerebral membranes may be greatly delayed and perhaps altogether prevented, so that the early diagnosis by the methods described below is of the greatest practical importance.

In 1903-4 Dutton and Todd further studied trypanosome infections in the Congo, and examined the blood of 1172 persons, many of whom were healthy, finding trypanosomes in 57, of which 34 were met with among 157 patients admitted to the native hospital. The disease was therefore found to be considerably more prevalent in the Congo than in Senegambia. They note that, even in advanced cases of sleeping sickness, somnolency was rarely seen, in which respects their account differs from those of the earlier reports from Uganda, but this appears to be due to many atypical cases being detected by routine blood examinations, which might otherwise have been overlooked, for in the later published cases from East Africa, sleepiness is also less conspicuous than in the earlier accounts. They did not meet with any such epidemic manifestations in the Congo as that unhappily prevalent on the shores of the great East African lakes, so that, like kala-azar, the disease is sporadic in those parts which have long been affected, but epidemic in newly attacked countries, into which it has been carried by the great extension of traffic—the first result of the so-called civilization of newly-opened-up countries.

To revert to the work of the First Royal Society Sleeping Sickness Commission in

Uganda, C. Christy carefully studied the spread of the disease in Uganda, and found that it extended both east and west from Busoga, affecting especially the shores and islands of the lake, but not extending very far from the water, except as imported cases. The area affected did not correspond in any way with the distribution of the *Filaria perstans*, for sleeping sickness has extended into Kavirondo, to the east of the great lake, where *Filaria perstans* is not found, while it is absent from large areas to the north of the lake in which that *Filaria* is very common: Manson's hypothesis that the two are causally related is thus disproved. Christy suggests that the disease was brought to Uganda by followers of Emin Pasha's Sudanese soldiers. The most important additions to our knowledge, however, we owe to Colonel Sir David Bruce and his colleagues Nabarro and Greig, who constituted the Second Commission of the Royal Society.

The results may be summed up in Bruce's conclusion that "Sleeping sickness is, in short, a human tsetse-fly disease." Although Castellani first found the trypanosome in the cerebro-spinal fluid in sleeping sickness, yet, according to the Second Commission, "he did not consider that this trypanosome had any causal relationship to the disease, but thought it was an accidental concomitant like *Filaria perstans*," as he had cultivated cocci from the cerebro-spinal fluid, which he considered to be the cause of sleeping sickness. Bruce, who had discovered the trypanosome of tsetse-fly disease in South African cattle some years before, at once recognized the significance of such an organism in sleeping sickness, and soon proved that trypanosomes were present in the cerebro-spinal fluid of every case of the disease, and also in the peripheral blood in practically all, while they were absent in other affections. Moreover, in the sleeping-sickness areas 28·7 per cent of 80 natives showed a trypanosome similar to that of sleeping sickness in their blood, but in a non-sleeping-sickness area 117 examinations gave no positive result. Further, the subcutaneous injection into monkeys of trypanosomes obtained from the blood of patients showing no symptoms of sleeping sickness, and those from the cerebro-spinal fluid of undoubtedly cases, both gave rise to a similar disease, which in its later stages clinically resembled sleeping sickness, and was then accompanied by the presence of the organism in the cerebro-spinal fluid of these animals. Later, Dutton, Todd and other Liverpool workers showed that the animal reactions of trypanosomes from the blood and the cerebro-spinal system respectively are identical, and differ from those of cattle tsetse-fly disease in not being lethal to the latter animals.

Bruce next set to work to see if the distribution of sleeping sickness corresponded to that of any particular insect which might carry the infection, and found that it was in very close agreement with that of a tsetse fly, the *Glossina palpalis*. Further, it was proved that these flies, when fed on the blood of sleeping-sickness patients and then caused to bite monkeys, conveyed the disease to them. Lastly, the same species of flies caught in localities badly infected with sleeping sickness also produced the disease in monkeys on which they were fed, thus completing the evidence that trypanosomiasis, including its later complication of the nervous system producing the symptoms of sleeping sickness, is a human tsetse-fly disease.

Much work has been done to ascertain if any developmental stage of the *T. gambiense* takes place in the alimentary canal of the tsetse fly. Bruce originally proved that another variety of tsetse fly, *Glossina morsitans*, can carry the infection of the cattle disease up to

forty-eight hours after being fed on an infected animal, but not longer. In 1901 (*Proc. Roy. Soc.*) I found that the trypanosome of surra in Indian horses could be mechanically conveyed from one animal to another by the bites of horse flies (Tabanidae), an observation which has been confirmed in the Philippine Islands and elsewhere. Koch and also Gray and Tulloch found great numbers of trypanosomes in the alimentary canal of tsetse flies fed on sleeping-sickness patients, which they considered to be developmental forms of *T. gambiense*, but later Professor E. A. Minchin, in working in Uganda with Gray and Tulloch, found that these forms belonged to two species of trypanosomes, which were quite distinct from *T. gambiense*, while the latter died out of the alimentary tract of the flies within four days, no development occurring during this time. They further showed that in the case of a cattle trypanosomiasis, tsetse flies, after biting an infected animal, could carry the infection to only the first animal subsequently bitten, but never to a second one. This indicated that the trypanosomes had remained alive in the proboscis of the fly, and were washed out at the first bite, but no regurgitation of the organisms in the proventriculus subsequently occurred, which might infect a second animal. This infection was purely mechanical, as I had found it to be in the case of surra trypanosomes carried by tabanidae.

Development of *T. gambiense* in Tsetse Flies.—Further experimental work was therefore done in which much care was taken to avoid the fallacies of early experiments due to caught flies being already infected with one of the numerous trypanosomes met with in various forms of animal life in Africa. During 1909 a valuable series of papers have been published by Kleine giving the results of very extensive experiments with home-bred flies in an area free from *T. gambiense* infection. On emergence from the pupa they were fed for four days on infected monkeys and afterwards on healthy ones until the latter showed trypanosomes. Then small groups of the infected series of flies were fed a few times on different healthy monkeys, the flies being finally killed and examined for trypanosomes. He found that only those monkeys developed the disease which had been fed on by one or more flies containing trypanosomes. He estimated that 10 per cent of bred flies fed on diseased animals became infected with trypanosomes. The intestine always contained them, the proventriculus generally, while they were occasionally also seen in the proboscis and salivary glands. Fifty control flies fed on healthy animals remained free from trypanosomes. The important point in these experiments is that the infection occurred from twenty to sixty-six days or more after the flies had been fed on the diseased animals, so that the trypanosomes found in them were clearly developmental forms. Moreover, he obtained no mechanical transmission of infection by the bites of 1910 tsetse flies fed on healthy animals eighteen to twenty-four hours after sucking infected blood, so the direct conveyance of infection is of very brief duration.

Sir David Bruce and his colleagues again took up the investigation and soon confirmed Kleine's observations with a most instructive experiment in which a tsetse fly became infective twenty days after feeding on infected monkeys and subsequently conveyed the disease by its bites to a series of healthy monkeys up to seventy-five days after it had been first fed. It then died, and on dissection its gut was found to be crammed with innumerable trypanosomes, and in addition the salivary glands contained a large number,

thus fully accounting for its dangerously infective powers. The development of human trypanosomes in tsetse flies and infection through their bites from the salivary glands was thus finally established.

The Discovery of a Second Form of African Sleeping Sickness.—In 1910 J. W. W. Stephens of the Liverpool School of Tropical Medicine noticed a peculiarity in the morphology of a trypanosome obtained from the blood of a European patient from North-Eastern Rhodesia, which consisted in the occurrence of short stumpy forms with the macro-nucleus near the posterior end of the organism, and further study with Fantham led them to describe it as a new species under the name of *Trypanosoma rhodesiense*. In the following year Sir David Bruce led another Royal Society Commission to investigate the matter in Nyassaland, and soon confirmed Stephens' view that the disease there was distinct from the long-known Congo sleeping sickness. Bruce found the same trypanosome in the blood of numerous wild animals, and being struck with its resemblance to that of Nagana, which he had discovered in animals in Zululand as far back as 1894, he obtained a strain from that country, and showed that in its morphology, animal infections and development in *Glossina morsitans* the newly named *T. gambiense* was indeed nothing but his old friend *T. brucei*, so the latter name stands and the new one disappears from nomenclature unless future work upsets Bruce's authoritative conclusions regarding it. We therefore have to deal with Congo sleeping sickness caused by the *T. gambiense* and carried by the bites of *Glossina palpalis*, and Nyassaland sleeping sickness due to *T. brucei* and carried by *Glossina morsitans*. As the latter fly is most widely distributed in Africa, and the Nyassaland form of human trypanosomiasis is far more rapid in its course and more deadly even than its Congo ally, the distinction is an important one.

Geographical Distribution of Sleeping Sickness.—Bruce in 1915 gave the following distribution of the two forms of sleeping sickness. The Congo variety extended on the north from St. Louis, Senegal, to the Bahr-el-Ghazal in the Egyptian Sudan ; on the east to the eastern shore of the Victoria Nyanza ; on the south to the southern end of Lake Tanganyika, the river Luapula in North-Western Rhodesia and Donguela in Portuguese West Africa. The Nyassaland form had then only been found in that country and in Rhodesia, although likely to be met with far beyond those areas on account of the much wider distribution of *G. morsitans* and reservoirs of infected game.

ETIOLOGY

The somewhat lengthy history of the highly interesting investigations, which have done so much to clear up the mystery formerly surrounding the deadly sleeping sickness and will always be most closely associated with the name of Bruce, will have served to make clear the main points in the etiology of the disease, but the parasite and its carrier remain to be described.

The Trypanosomes of Sleeping Sickness and their Differentiation from Animal Forms.—In Central Africa there are few forms of animal life from crocodiles to flies which are

not infected with some stage or other of trypanosomes, and it is only recently that any scientific classification of them has been put forward. That of Bruce is both simple and practical, being based on the mode of development of the protozoal parasite in the tsetse flies, which carry the infection from one animal to another, while each class also have well-marked microscopical appearances. For convenience of reference I have embodied the main features of distinction between the three classes in the accompanying table, which will allow of their being readily grasped, so a detailed description is unnecessary.

BRUCE'S CLASSIFICATION OF AFRICAN TRYPANOSOMES IN MAN AND DOMESTIC ANIMALS

Groups and Names.	Morphology.	Pathogenicity for Animals.	Mode of Development in Tsetse Flies.
A. BRUCEI GROUP— 1. <i>T. brucei</i> 2. <i>T. gambiense</i> 3. <i>T. evansi</i> 4. <i>T. equiperdum</i>	Polymorphic, varying from short stumpy flagella-free to long slender forms with flagella. Cytoplasm with many dark staining granules. Micronucleus small and at some distance from posterior end. Undulating membrane well developed and folded. Shape distinctive.	Affects many animals, including man, horses, cattle, dogs and most of the smaller experimental animals.	At first in the intestine, later passes to salivary gland through the proboscis and there completes the development of the infective forms.
B. PECORUM GROUP— 1. <i>T. pecorum</i> 2. <i>T. simiae</i>	Small and monomorphic. Cytoplasm not granular. Micronucleus prominent, subterminal, and may seem to project beyond margin. Undulating membrane fairly well developed.	<i>T. pecorum</i> causes important disease of cattle. <i>T. simiae</i> kills pigs rapidly.	Begins in the intestinal tracts and later passes forward into the proboscis to reach the salivary duct or hypopharynx, but not the salivary glands.
C. VIVAX GROUP— 1. <i>T. vivax</i> 2. <i>T. caprae</i> 3. <i>T. uniforme</i>	Monomorphic with very rapid movements. Posterior extremity enlarged. Cytoplasm clear and hyaline. Micronucleus large and terminal. Undulating membrane little developed and simple.	Only affects horses, cattle, goats and sheep. Monkeys, dogs, rabbits, guinea-pigs and rats are refractory.	At first only in the labial cavity of the proboscis, and later in the salivary duct or hypopharynx. No development in intestinal tract or salivary glands.

The first group, *T. brucei* group, is the only one in which the infective forms invade the salivary glands, while they are polymorphic, varying much in shape and size. It

Plaque 6. — Mr. Sir David Bruce's Lecture on "Trypanosomes" in the Lecture of June 1912.

Fig. 9. The testes fly, life size.

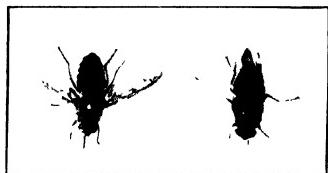


Fig. 8. — *Trypanosoma nana*. — x about 200.

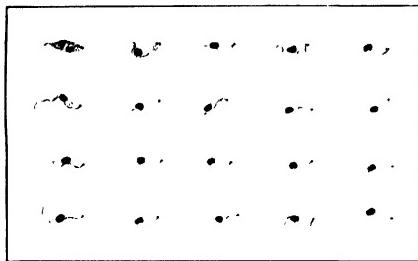


Fig. 7. — *Trypanosoma evansi* (Klebs). — x about 200.

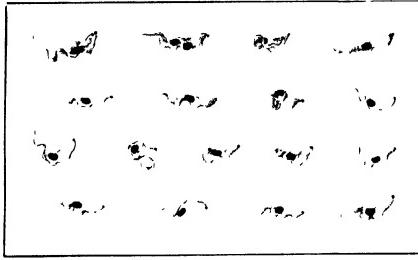


Fig. 6. — *Trypanosoma trivittatum* (Fleming). — x about 200.

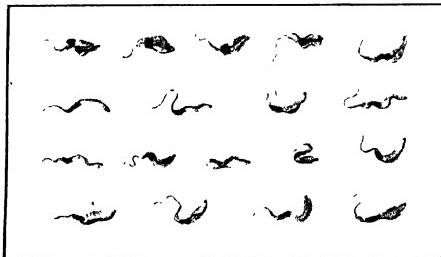


Fig. 5. — *Trypanosoma simiae*. — x about 200.

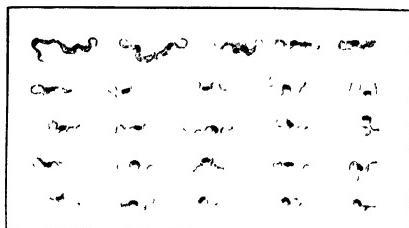


Fig. 4. — *Trypanosoma pectorale*. — x about 200.

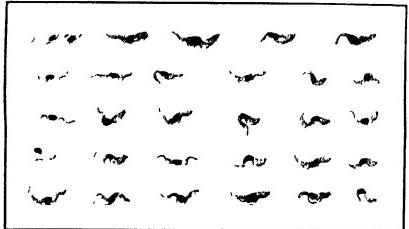


Fig. 3. — *Trypanosoma equinum* (Dutton). — x about 200. — Tragically dead.

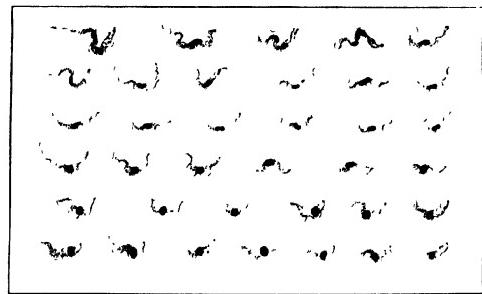
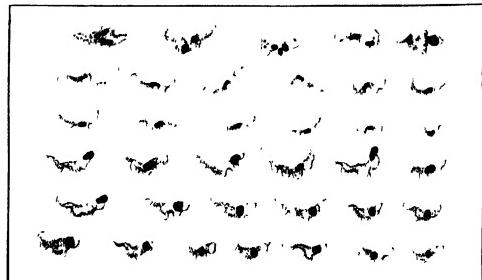


Fig. 2. — *Trypanosoma lewisi* (Pilimoor and Bradford). — x about 200. — Zimbabwe, 1912.



includes the two African human forms and two northern African animal forms, which have similar morphology and animal reactions. The second group, *T. pecorum* group, are small and monomorphic, and develop in the intestinal canal of insects and reach the proboscis, but not the salivary glands; while the third group, *T. vivax* group, are extremely active in their movements, but only develop in the labial cavity and proboscis at first and later in the salivary duct or hypopharynx. The last two groups only affect animals. The accompanying illustration, taken from Sir David Bruce's Croonian Lectures, well illustrates the morphology of the principal forms. *T. gambiense* is very similar in appearance to *T. brucei*, but careful examination of a number of the organisms enables the latter to be distinguished by the presence of blunt-ended, posterior nucleated forms, which are quite common in the blood of animals infected by this parasite, but absent from those inoculated with *T. gambiense*.

Cultivation of Trypanosomes on Artificial Media.—In 1903 Novy and MacNeal cultivated the *Trypanosoma lewisi* on nutrient agar with a little peptone, to which a varying proportion of defibrinated rabbit's blood was added. The organisms grew in the water of condensation at either room temperature or at 37° F. In the same year they cultivated *Trypanosoma brucei* at 25° F., at least as much blood as agar being used. MacNeal later recommended the following as the best culture medium :

Extractives of 12.5 g. chopped beef in distilled water	1000 c.c.
Agar	20 g.
Peptone	20 g.
Common salt	5 g.
Normal solution sodium carbonate	10 c.c.

The organisms at first decrease, but in successful attempts they multiply again about the twentieth to thirtieth day, and can then be transplanted, a constant temperature of 25° C. being best. In this way in birds they could find trypanosomes frequently when they had failed to do so microscopically. Thomas and Breinl kept *T. gambiense* alive on blood agar for 68 days, but it lost its infectivity after 17 days. Gray and Tulloch were less successful, and the method has not yet become an aid in diagnosis of sleeping sickness on account of its uncertainty.

Glossina palpalis ; the Carrier of the *Trypanosoma gambiense* ; its Distribution and Habits.—Now that it is clear that the occurrence of sleeping sickness is so intimately related to the distribution of a particular species of tsetse fly, the *Glossina palpalis*, while the infection is probably rarely carried by other biting insects, even other varieties of tsetse flies, the distribution and life history of this dangerous species has become of the greatest importance in the prophylaxis of the disease. If Africa could be purged of this fly, sleeping sickness would probably soon cease to exist, just as the annihilation of all anopheles in a country or island would prevent malaria. Unfortunately the task in either case is usually impossible, yet much may be done by reducing the number of the pests, or by protecting against their bites.

The *Glossina*, or tsetse fly, is a blood-sucking genus peculiar to tropical Africa. The flies are brownish or greyish brown in colour with a prominent proboscis. In the male the

external genitalia form a prominent knob beneath the end of the abdomen. When in the resting position they can be distinguished from all other blood-sucking diptera by the fact that the brownish wings lie closed flat over one another down the back, like the blades of a pair of scissors, while the proboscis, ensheathed in the palpi, projects horizontally in front of the head. The closed wings extend behind the body of the fly, giving it an elongated appearance. On the other hand, in *Stomoxys* the prominent proboscis is not ensheathed in palpi, and is much more slender than that of *Glossina*, while they are also much smaller, and the closed wings diverge at an angle like those of the common house fly. A genus of small horse flies, the *Haematopota*, also somewhat closely resembles *Glossina* when at rest, but here again the wings do not close over one another, but meet together at the base, like the roof of a house, while they diverge slightly at the tips. The other genera of biting flies differ still more widely from the *Glossina*.

The *Glossina palpalis* itself differs from the seven other known species in that its body is almost black, with the exception of a pale patch on the dorsum of the abdomen, while the black colour of all five segments (tarsi) of the hindmost pair of legs is also characteristic. The colour of the abdomen in nearly all the other species is of a paler shade marked with sharply defined dark brown bands, which are interrupted in the middle line. Reproduction takes place by the female dropping a single larva at a time, which creeps into loose earth (or the crevice in a plant when laid in shrubs or palms) and in a few hours becomes a pupa, the perfect insect emerging from the chrysalis after five or six weeks. The female fly may certainly live for three months and drop from eight to ten larvae at intervals of about ten days. The pupae of *G. palpalis* were first found in nature by Dr. A. G. Bagshawe in 1906 on the shores of Lake George in Uganda. The usual position was at a depth of $\frac{1}{2}$ to 1 inch in light soil within 10 to 25 yards of water, in the shelter of banana plants or shrubs, generally on a sloping bank. On the West Coast of Africa, with its much heavier rainfall, Zuspitza found them in the forks of trees or in cracks in the bark and in the angles of the leaf-sheaths of palms at a height of from a few inches to 10 feet from the ground. Prolonged humidity or immersion in water, as well as exposure to the sun, killed the pupae.

Conditions affecting the Distribution of *Glossina palpalis*.—The fly is found from sea-level up to about 4000 feet near the Equator, but at lesser elevations in higher latitudes. It only occurs close to open water where there is also shade. In swampy reed-grown lakes or rivers it does not flourish. The shade of shrubs, trees, or long grass is essential for it. They are more numerous in the rainy season, and much decrease soon after the dry period sets in. A high degree of air moisture is favourable to it, so it is very abundant on the north-west shore of the Victoria Nyanza, which is kept damp by the south-east wind across the lake, while it is absent from most of the much drier south-east shore. It extends up along the banks of open rivers running into the great lakes, but ceases abruptly on the high escarpment to the east of Uganda. More important still is the fact that the fly is not as a rule found more than 20 yards from water, but if forest or brushwood extend far from the water's edge the range of the insect is more extended. Moreover they will follow native carriers for 300 yards, or rarely even farther from the water if the track is well shaded, and they may thus reach villages at some little distance from rivers or lakes.

Railway trains may convey them many miles, while they can also be carried by natives in canoes. They travel long distances along the banks of rivers. *Glossina palpalis* as a rule only appears during the daytime, being most abundant between the hours of 10 A.M. and 4.30 P.M., especially in shady places, but may be found in smaller numbers from sunrise to sunset. They may sometimes be met with in bright moonlight. In cloudy weather few are found, even a single cloud at once diminishing the numbers, they are not seen during rain, and wind also at once drives them to take shelter. They prefer both a black skin and dark clothes to those of a light colour, so they usually attack natives in preference to Europeans if both are present. Their bites are like sharp pricks and cause a moderate degree of after-irritation. They only exceptionally bite through clothes. They do not buzz, but strike directly at the part exposed--generally the back of the neck. Austen, and all other writers, are agreed that *Glossina* can only live on vertebrate blood, and cannot be supported on vegetable juices. In captivity they require to be fed every two days to keep them well, but Stuhlmann found that after a full feed they might still retain their weight before sucking blood for six to eight days, so that they probably can exist even longer in nature on a single feed. Koch examined the blood in a large number of flies, and found it to be that of crocodiles in 62 per cent, and human in the remainder. He has therefore suggested that these reptiles should be destroyed in order to cut off the principal food supply of the flies. Even if practicable this measure would not be likely to be of much use, as *Glossina palpalis* flourishes where no crocodiles are found. Lizards, birds, etc., also furnish food for the flies. It is also generally agreed that *G. palpalis* is not dependent on big game, as *G. morsitans* so largely is.

Geographical Distribution.--The *Glossina palpalis* has a very wide distribution throughout the large area of African continent comprised roughly in the zoological division known as the Western Equatorial region. To the north it has been found up to 15° in Senegambia, and to 8° in the Anglo-Egyptian Sudan on the Nile. To the south it reaches to 12° on the Luapula River in North-Eastern Rhodesia, and about the same level in Portuguese West Africa. In 1861 three specimens were taken on the Zambesi River, although it is not found there at the present time, so that its distribution may alter, and it may yet be discovered beyond the above-mentioned latitudes. The countries in which it has been recorded comprise all the West Coast settlements from French Senegambia and British Nigeria in the north, through the Gulf of Guinea and the Congo watershed to Portuguese Angola in the south, this tract having been the original home of sporadic sleeping sickness for over one hundred years. From here the disease was doubtless carried by caravans to the Upper Nile basin, where the *Glossina palpalis* is to be found on the shores of the Victoria, Albert Edward, and George lakes, and the tributaries of the Nile arising from them. It also has been found on Lake Rudolph to the north-west of Lake Victoria, and also on Tanganyika and Mweru in the extreme north-east of Rhodesia, but not on Nyassa and Bangweolo a little farther south. It has been reported to be absent from Lake Chad and from Kivu, immediately to the north of Tanganyika. The east coast is free from the fly for a width of 400 miles, the high escarpment to the east of the great central lake system forming the dividing line. This is a most important fact, as in the absence of *G. palpalis* sleeping sickness is extremely unlikely to become indigenous

in the East African coast area. This forms a great safeguard against the affection being carried to India and other countries, while, as the *Glossina* is limited to Africa, there is little or no danger of the spread of sleeping sickness in tropical Asia, just as it has failed to become indigenous in the West Indies, although imported cases have frequently been seen there.

The Cycle of the Development of Infective Forms of Trypanosomes in *Glossina palpalis* has been described by Bruce as follows. For the first three or four days after feeding on infected blood trypanosomes are found in all the flies, although experimental injection of broken-up flies into susceptible animals shows that they are only infective up to about eighteen hours. When digestion is completed after six or seven days the parasites have disappeared from some 95 per cent of them, while it is only in the remaining 5 per cent that any further development takes place, probably from some especially resisting organisms. In these rapid multiplication takes place until the gut is filled with countless swarms of organisms, which are long, moderately broad, uniformly staining trypanosomes with central oval nucleus and a small round micronucleus at some distance from the elongated posterior extremity, while the undulating membrane is simple and the flagellum very short, proceeding little if at all beyond the protoplasm of the cell, while it often arises from a pink-coloured body near the micronucleus, an appearance never seen in the normal blood trypanosome. This appears to be similar to the eosin-staining body I found in the development of the flagellate stage of the parasite of kala-azar (see p. 12). This is the predominating form in the intestine, although very various shapes are seen. The trypanosomes do not appear until the twenty-fifth day in the salivary glands, which they reach by way of the proboscis and salivary duct or hypopharynx, as they have never been seen in the body cavity. They now revert to the original blood form and become infective, probably remaining so for the rest of the life of the fly, as these insects have been proved to retain their infectivity up to ninety-six days, while in but few cases was there any evidence of their again becoming harmless.

When tsetse flies, caught wild, are found to be infective for animals it is probable that the cycle of development of the trypanosome has taken place in them. The proportion of such flies on the northern shores of the Victoria Nyanza lake in Uganda at the time of the epidemic of sleeping sickness was found to be as high as 11·2 per thousand, but a year after the population had been removed it had fallen to 1·2 per thousand, and five years after the removal 1·8 per thousand of flies were still infective, while from 1909 to 1912 the figure remained between 0·4 and 0·04, showing that the depopulation of the area had not completely removed the infectivity of the flies as had been expected, and indicating some still undiscovered factor in its maintenance.

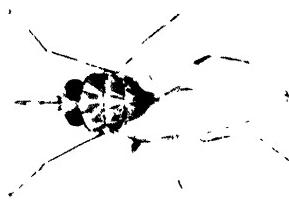
This was eventually found to be an **animal reservoir** in the form of infection of the only common species of antelope of the district, the sitatunga (*Tragelaphus spekei*), while cattle were also proved to be possible reservoirs of the infecting trypanosome. This important fact greatly increases the difficulties of prophylactic measures in fly-infested areas.

***Glossina morsitans* the Carrier of *Trypanosoma brucei* of Nyassaland Sleeping Sickness.**—The main facts regarding this are similar to those already detailed in the case of the

The Tsetse Fly (*Glossina morsitans*)

Plat 7

Trypanosoma Gambiense, from rat's blood.



Glossina palpalis, so only the more important points of difference need be noted. In its habits it differs considerably in being a fly of the dry thorny scrub, which covers such large areas of tropical Africa, so is found away from water, but requires shade and is absent from open plains exposed to the tropical sun—an important point, as deforestation and cultivation drive out this dangerous pest. The flies appear during the heat of the day and will, especially the male flies, follow moving objects, such as a cyclist. They feed about once in five or six days mainly on the blood of antelopes, as shown by examinations of the blood found in them, and never suck the juices of vegetables. When game has been destroyed by outbreaks of rinderpest tsetse flies disappear for a time, indicating that the removal of game is likely to free a district from the danger of the deadly Nyassaland form of sleeping sickness. The fly feeds rapidly, fully distending itself in within a minute. From the single larva laid by the female the fly emerges within from twenty-three days at a temperature of 85° F., to sixty days at 65° F. Bruce found that the infectivity for animals of wild flies was a minimum of 1 in 500, so that in the Nyassaland sleeping-sickness area it is 500 to 1 against the bite of a single fly infecting man. The development of the *T. brucei* parasite in the fly is precisely similar to that of *T. gambiense* in *G. palpalis* already described. *G. morsitans* is extremely widely distributed through nearly all parts of Central Africa far beyond the present known limits of Nyassaland sleeping sickness, so there is great danger of that deadly form of the disease spreading to other parts. Further, the **animal reservoir** is also much more extensive, as many forms of antelope are infected, especially the waterbuck, hartebeeste, reedbuck, and duiker, 7·8 per cent showing infection.

PROPHYLAXIS

The great recent extension of our knowledge of the etiology of sleeping sickness has opened up the way to the adoption of practical preventative measures, both as regards the ravages of the disease in already infected areas and its extension to those still free, but which are known to be potentially dangerous on account of their being infested with *Glossina palpalis*. As in the case of other insect-borne diseases, notably malaria, there are several links in the chain of infection open to attack, which may be conveniently considered under the following headings.

Destruction of the *Glossina palpalis*.—As it now appears certain that this fly alone is intimately associated with the spread of human trypanosomiasis, any measures which will eradicate it from an infected area should lead to the disappearance of the disease as soon as the already infected persons have died or recovered. Unfortunately, in the present stage of civilization in tropical Africa, such a measure is as impossible as the analogous problem of ridding extensive rural areas of anopheles at any practically feasible cost. Fortunately, however, the *Glossina* but rarely travels more than a few score of yards from open water, while it requires the shade of trees and bushes, or at least long grass, to afford the shelter which is essential to it. Advantage has been widely taken of this fact of its life history in Uganda and elsewhere, to clear the fly-infested scrub for a width of 30 or 40 yards from the river or lake bank. As it is essential that the bush should not be allowed to spring up again, it must be removed or burnt and the roots dug out; some crop should

now be planted to occupy the cleared ground, the best being Citronella grass, the smell of which is said by some to be disliked by the flies, while it has a commercial value. The lower branches of large trees should be stripped, but they should not all be destroyed, especially at ferries and fords, because unless some shade is left in the cleared area the natives will not remain in the sun, but seek the neighbouring fly-infested bush beyond the clearing. The places which should be thus cleared are landing-places on lakes and rivers, fords, camps, markets and villages close to the water's edge. The strip should extend for from one to three hundred yards along the water's edge on each side. It is also well to clear the scrub for several hundred yards along tracks leading from water to villages, leaving only large trees for shade.

These measures lessen materially the danger of the people being bitten by the flies, and are reported as having given good results in Nyassaland and the island of Principe in Portuguese West Africa, but to have largely failed in Ashanti. In the first-named place Hearsay also provided public latrines to save the natives from having to go into fly-infested jungle for that purpose. Forest fires also help to reduce the flies by killing the pupae, while in Senegal more extensive forest clearing is advised. Direct destruction of the flies by means of trapping has also been largely resorted to. Mechanical traps in fixed places have proved of little use for this purpose, and are now seldom heard of, but advantage has been taken of the attraction for tsetse flies of moving objects and black surfaces to trap them with sticky bird-lime mixtures, such as cocoa-nut oil and resin, now supplied by Tunbridge and Wright of Reading to Principe, where between 1911 and 1913 no less than 470,000 flies have been caught, and these dangerous insects have been nearly exterminated by this measure and jungle clearing. The plan adopted is to clothe natives from head to foot in white with a black lime-smeared patch on their backs, and to send them in pairs into the fly-infested jungle. Artificial breeding-places in the form of felled trees, under which the pupae are laid and later destroyed with fire, have been used by Lamborn in Nyassaland.

Destruction of the Animal Reservoir in the Form of Wild Game and certain Susceptible Domestic Animals.—Now that it has been shown that antelopes are commonly infected with both the human forms of trypanosomes and thus form natural reservoirs of the infection, the destruction of these graceful but dangerous animals in the neighbourhood of habitations has become a most essential necessity in the campaign against sleeping sickness, the greatest scourge of Central Africa, and one which is retarding the economic development of the country to a most serious degree. Yet in many parts the game laws actually prohibit the inhabitants from protecting their lives from this most insidious, but none the less real, danger, as if there were not still unlimited, uninhabited parts of Africa open for the delectation, without the aid of laws which are a danger to the native inhabitants, of those who have no better object in life than to slaughter noble animals. As Sir David Bruce has not too forcibly put it, "It is self-evident that these wild animals should not be allowed to live in fly country, where they constitute a standing danger to the native and domestic animals. It would be as reasonable to allow mad dogs to live and be protected by law in our English towns and villages. Not only should all game laws restricting their destruction in fly country be removed, but active measures should

be taken for their early and complete blotting out." And he notes that no pathogenic trypanosomes were found by the Commission in the blood of animals in fly-free areas. In Principe many wild pigs were killed, and the keeping of domestic animals in fly-infested areas was prohibited.

Removal of the Population from Fly Areas.—As the destruction neither of the parasite nor of its carrier is usually practicable on a large scale, some other measure may have to be adopted. In the case of sleeping sickness advantage has been taken of the very restricted areas in which the *Glossina palpalis* is found to remove the people from such places. Under the direction of Dr. A. Hodges, who has had several years' experience of the disease in Uganda, at the end of 1907 all the natives, whether infected or not, were cleared out of a two-mile strip all round the intensely infected north-western shore of the Victoria lake, with the loyal assistance of the chiefs, and only allowed to settle inland in fly-free areas. The infected fish-eating islanders could not be dealt with in this way, but they were only allowed to land at certain places on the mainland, which had been widely cleared of trees and bush so as to keep them free from tsetse flies. Camps for the treatment of the infected were started under medical officers, but no compulsion was used to get the people to enter them. The fame of the atoxyl treatment led many at first to come for treatment, but the numbers fell off when the results did not come up to the original expectations. The above radical measures seem likely to go far towards staying the appalling death-rate in the part of Uganda dealt with, and it is being now extended to a badly infected area in Southern Kavirondo on the north-east shore of Lake Victoria, which was first found to be infected in 1902. As a result of these measures the deaths from sleeping sickness have fallen from 8003 in 1905 to 1723 in 1908. The decrease has been most marked on the mainland, and less on the islands. On the other hand the original hope that the people might safely be permitted to return after a year or two has not been fulfilled, owing to the antelopes providing a natural reservoir of the infecting trypanosome.

In North-Eastern Rhodesia and Nyassaland sleeping sickness became serious at the south end of Lake Tanganyika, Lake Mweru, and the northern portion of the Luapula River. Clearings made in 1907 did not prove successful, so arrangements were made to move 12,000 people from 350 miles of infected border to places 15 miles inland, with the result that the extension of the disease was checked, as reported by May.

The Isolation and Treatment of the Sick and the Prevention of their Migration constitutes another powerful prophylactic measure by greatly lessening the number of infected persons in the villages, but is not always easy to enforce, especially in parts where the disease is very mild, as in Senegal and Ashanti, although more readily taken advantage of by the villagers in the case of the more rapidly fatal Nyassaland disease, and also used extensively in the important and successful campaign in Principe. When possible the sick should be isolated in a fly-proof area, or a wide clearing of jungle made around their camp. Prohibition of the movements of infected persons, even if not apparently ill, is a more difficult procedure depending on having a sufficient skilled staff to examine the people at different centres of trade, but it has been used, though for want of medical men in a much restricted manner, in connexion with defined infected areas in Belgian Congo.

In addition to the treatment of the actually sick in hospital, those in apparently good health who are found infected with trypanosomes are treated with a view to destroying most of the organisms in their circulation, and so lessening materially their infectivity for others. For this purpose atoxyl has been most largely used, one or two injections being found to cause the trypanosomes to disappear from the blood for several months according to some workers, although others have not found it so effective. One injection of salvarsan in doses of 0·01 gm. per kilo or neosalvarsan 0·013 gm. has been reported to clear the blood for from two to eight months, and salvarsan-copper 0·004 gm. per kilo to be effective as long as nineteen to twenty-four months in a few cases.

Results of Prophylactic Measures.—The good effect of moving the hut-tax labourers by the Uganda Government from the infected lake shore to a fly-free area has already been mentioned, and also similar measures in Nyassaland. At Kisantu in Belgian Congo two-thirds of the population were swept away within ten years up to 1910, but since 1912 the percentage of natives infected has fallen from 4·7 to 0·7 in 1915, and the birth-rate had begun to increase again. In the case of the island of Principe, where a Portuguese Commission laboured for several years under Da Costa, in 1908 no less than 23·5 per cent of the natives were infected, and the disease threatened to depopulate the island. In 1911 active prophylactic measures were commenced, which have already been referred to, and in 1913 the percentage had fallen to 3 and a year later to 1 per cent—a striking success which should serve as a great encouragement to other infected countries.

CLINICAL DESCRIPTION OF TRYPANOSOMIASIS

Owing to the absence of symptoms in the early stages, and the fact that the long duration of the disease makes it exceedingly difficult to follow up patients throughout its course, it is not easy to give a complete clinical description of trypanosomiasis. The following brief account is mainly based on an analysis I have made of the cases recorded by the Royal Society and Liverpool expeditions to Africa.

Early Stage with few or no Symptoms.—By examining the blood of a large number of apparently healthy persons in Senegambia and the Congo State, Dutton and Todd were able to study a number of cases of early trypanosomiasis, which were only recognizable by the parasites having been detected in their blood. A considerable proportion of them stated that they were in good health, and complained of no symptoms whatever. Others had occasional slight intermittent fever, accompanied by weakness, and sometimes an increased rapidity of both the pulse and respiration. A physical examination showed no constant signs or lesions, *with the all-important exception of general enlargement of the superficial lymphatic glands*. Neither the patients nor their friends had any suspicion that they were ill, nor did they show mental dulness or slowness of expression. Such cases can only be detected by an examination of the blood or lymphatic gland juice for active trypanosomes. Yet on their detection depend both the main hope of protecting them from the development of the later extension of the infection to the cerebro-spinal system, which constitutes the fatal sleeping sickness, and also the prevention of their carrying the disease germs into places which may have been previously uninfected.

Intermediate Stage with Mild Symptoms, but without the Cerebral Symptoms of Sleeping Sickness.—Dutton and Todd record cases of an intermediate type with irregular intermittent fever, occasionally becoming remittent or of a low continued type for a few days. The patient may be somewhat weak, but is usually well nourished, unless there is some other cause of wasting present. The superficial lymphatic glands, especially of the posterior triangles of the neck, are enlarged, but oedema and tremors are absent. The pulse and respirations may be quickened. There is as yet no sleepiness or marked mental dulness, although the patient may have become untidy and careless and be easily fatigued. In Europeans patches of an erythematous rash have been recorded in this stage by Sir P. Manson and others, together with transient oedema. The rash is an early symptom and usually has an annular or circinate appearance, and it has been found in nearly all European patients, but is difficult to detect in dark-skinned natives. Less commonly a nodular erythema occurs or little purple raised spots somewhat resembling blind boils.

This stage of blood and gland infection may continue for many months, or even for one or more years, but whenever it is possible to follow up such patients, they almost invariably eventually pass on into the deadly sleeping-sickness stage, as in those reported by the Royal Society Commission in Uganda already mentioned.

Stage of Cerebro-spinal Infection of Sleeping Sickness.—When at last the trypanosome finds its way into the arachnoid space and sets up a chronic form of cerebro-spinal meningitis, accompanied by a mononuclear cellular infiltration of the pia-arachnoid membranes and surface of the brain, then the mental changes ensue which constitute the essential symptoms of sleeping sickness. The disease now for the first time presents a fairly typical clinical picture, which becomes more and more characteristic as it progresses to its almost inevitably fatal termination.

Mental Condition.—In all the earlier accounts of the disease the most striking symptom was a tendency for the patient to go off to sleep at any time of the day, although he was easily roused from this condition. In the Congo State, however, Dutton and Todd found this symptom was quite an unusual one, while it may also be absent, especially in the less advanced stages, in the epidemic disease in Uganda. From an analysis of 50 cases of sleeping sickness recorded in the reports from both sides of Africa, I find that, on admission, by far the most usual mental condition was a marked dulness of the intellect, with slowness in answering questions, a vacant look, and an apathetic state. Actual sleepiness was much less frequent, although the tendency of the patient to lie about doing nothing, and taking no interest in his surroundings, may easily lead to his being thought to be actually asleep. He is, however, easily aroused, especially for meals, which he relishes highly. As the disease progresses the mental dulness deepens into actual drowsiness, and eventually he may become comatose during the last few days.

Other nervous symptoms which may be met with are a chronic mild form of mania; retraction of the head, and even opisthotonus. Loss of sexual power in man and amenorrhoea in women are common symptoms, which may be present in the early stage of blood infection long before the cerebro-spinal system is invaded by the trypanosomes. Under atoxyl treatment these symptoms may sometimes disappear. Orchitis has also been

met with in European patients. The reflexes appear to present no constant changes, being usually recorded as normal, while an increase or a decrease of the knee jerk was about equally frequent, and ankle clonus was occasionally recorded. In the later stages there may be great wasting of the muscles and extreme weakness with shuffling gait, but actual paralysis appears to be very exceptional. Rigidity of muscles may also occur.

Kerandel's Sign is a frequent and early symptom, appearing sometimes in the second or third month of the disease. It consists of deep hyperesthesia elicited when the soft tissues are sharply compressed by a squeeze or a blow, which produces a sharp pain quite out of proportion to the force applied and continuing for a few seconds, while it may be so great as to force a cry from the patient. Kerandel himself suffered from it and considered it pathognomonic of the disease, while it disappears with improvement under treatment.

Tremor is a very constant and important symptom, being most often seen in the tongue. It occurs next most frequently in the hands, and may extend to any part of the body in advanced cases. The fine tremor of the tongue is one of the most constant symptoms of the disease when it has reached a fairly typical condition, and has been used to define a particular stage of the affection. Ranken noted general tremor in 7 per cent, tongue tremor in 37 per cent, and tremor of the hands in 9 per cent on admission to a camp in the Sudan.

Headache is also frequently present, and may be noted in an early stage. Pains and hyperesthesia in various parts of the body are also not infrequently recorded. Post mortem the pia-arachnoid membrane presents a ground-glass-like appearance. The cerebro-spinal fluid is usually clear, but may be slightly turgid and in excess. Microscopically there is a marked mononuclear infiltration of the membranes, which extends along the perivascular spaces into the brain substance, as described by Mott.

The Temperature Curve.—The pyrexia of trypanosomiasis is very variable and appears to present no characteristic features. Several writers have recorded a sudden onset of the disease with rigors and high fever. Fever may be absent altogether for considerable periods in all stages of the disease. The published charts show that it is most frequently of an intermittent type, usually rising to 100° or 101° only in the evening, and being normal or subnormal in the morning. It may occasionally assume a remittent type, but as a rule only for a few days at a time, while it rarely or never shows a high continued type. It may sometimes for a time be of a low continued type, that is, falling below 101°, but not varying over more than 2° daily. There is no constant relationship between the rises of temperature and the presence of trypanosomes in the blood, but they are more often present during pyrexia than in its absence, while the fever may sometimes be associated with an increase of the parasites in the cerebro-spinal fluid. In the last stage of sleeping sickness the temperature is nearly always subnormal, and often markedly so for days or even weeks at a time, and it is at this time that the secondary invasion of cocci or the bacillus coli communis commonly takes place. On the whole the temperature curve appears to be of very little diagnostic value.

The Circulatory System.—The heart itself shows no important change, but the pulse is stated by several observers to be unusually rapid in proportion to the degree of pyrexia present, and this may be the case in the early stage of trypanosomiasis, before the nervous system has become implicated. This symptom, however, is far from being constantly marked, for out of 30 cases, in which the pulse was recorded on admission, in 21 it did not exceed 100 beats a minute, in 3 it was from 100 to 119, and in 6 reached 120 or over. It was most frequently between 80 and 90. It is of low tension and small. Lagane records 2 cases showing bradycardia with pulse-rates of 50 to 58 and 50 to 62. Oedema is a common symptom. Ranken noted oedema of the eyes in 18 per cent, while Hearsay found oedema of some part of the body in 10 out of 12 cases.

Respiratory System.—The lungs are also usually normal, except for occasional terminal complications. The respirations are said to be rapid, but in only 3 out of 13 cases noted on admission did the rate exceed 20 per minute. Slight bronchitis was noted in a few of the Congo cases as a complication, and some congestion was frequently found post mortem, but in only 2 out of 36 autopsies I have analysed was actual pneumonic consolidation found, and in another some pleurisy. Dutton and Todd also record gangrene of the lung and localized tubercle of the organ as terminal complications.

Liver.—No affection of the liver appears to be produced by the trypanosomes. In 27 out of 33 cases the organ was recorded as being normal, and in the remaining 6 slight enlargement was present, but this was usually of malarial origin. In 5 post-mortems some degree of cirrhosis was found, but it is not clear whether this was due to the trypanosome infection, malaria, or other cause.

The Spleen.—In 12 out of 33 cases the spleen was to be felt below the ribs, but it very rarely showed marked enlargement. Post mortem, in two-thirds of the cases showing increased size of the spleen, malarial pigmentation was present, and in the remainder the organ was only slightly in excess of the normal, and presented a congested appearance, the enlargement being thus commonly malarial in origin, so that at any rate no great increase of the organ is produced by trypanosome infection. In several cases in which spleen puncture was recorded, only a few of the parasites were found, so that the trypanosomes do not appear to accumulate in this organ, and its puncture is of less diagnostic value than the simpler and much less dangerous aspiration of the lymph glands.

Lymphatic Glands.—The constant and early enlargement of the superficial lymphatic glands has been already mentioned as the most important physical sign in the disease. They are usually firm, but with an elastic feel, independent of each other and not adherent to the surrounding structures, and are painless. Gray and Tulloch described them as soft with the consistence of a ripe damson. The Portuguese Commission found some enlargement of the lymphatic glands in every one of 70 cases, while in 52 there was a general invasion of the lymphatic glandular system. In the last stages they may show coccal infection, and in consequence undergo softening, especially the femorals, as a result of chigoe parasites in the feet. Unsoftened glands may also show coccal infection when this is of a general nature during the last few days of life. The enlarged glands always contain numerous trypanosomes in all stages of the disease, even when they are absent

from the circulating blood, and thus afford an easy method of verifying the diagnosis by obtaining the parasite from them. Hence their practical importance cannot be exaggerated. In the great majority of cases the enlargement is a general one, but the posterior cervical glands are specially frequently involved, which is a point of great value on account of their ready accessibility. I only found one case in those analysed in which the cervical glands are recorded as not being enlarged.

The Tongue presents no characteristic features, although it is commonly furred during fever.

The Bowels are most frequently constipated, but diarrhoea and dysentery may occur as complications.

Sickness is not often mentioned in the clinical histories, although Greig and Gray record several cases in which peculiar petechial haemorrhages and superficial erosion of the mucous membrane were found post mortem.

The Urine presents no important changes, neither albumen nor sugar having been recorded on admission in the series analysed.

Eye Complications have frequently been met with. Daniels noted them in 12 out of 32 cases, or 37.5 per cent, and describes them as essentially a toxic iridocyclitis with a varying amount of keratitis, conjunctivitis, circum-corneal congestion and photophobia. These may be early symptoms and be the first cause of the patient seeking medical advice. Similar cases have been described by others.

Progress and Terminal Complications.—The course of the disease is very variable, but once the arachnoid space has been invaded by the trypanosomes, its advance is much more rapid. In the recorded cases the duration of the disease after definite symptoms of illness had appeared, varied from three to nine months, although it may occasionally be longer or shorter than that period. Progressive weakness and emaciation are observed, causing the patient to become bedridden. Temporary marked improvements may occur, but they are not of long duration, and once the cerebro-spinal fluid is found to contain the parasites the downhill course is usually a steady one.

Various terminal complications may finally ensue; 13 out of 22 post-mortems on the Congo showed lung complication, septic infection or dysentery. In the epidemic disease in East Africa such complications appear to have been less common, but in 7 out of 16 post-mortems recorded by Greig and Gray a general infection with a diplococcus was proved by cultures from the cerebro-spinal fluid, heart blood and lymphatic glands. As in several of them punctures made only a few days before death showed no such organisms, the complication must have occurred very shortly before death. In the remainder the trypanosomes alone appear to have produced the fatal termination.

Age and Sex Incidence.—Todd among 79 cases in Gambia found 76 per cent to be adults, including 39.3 per cent males and 36.7 per cent females. Of 24 per cent in children 16.4 per cent were boys and 7.6 per cent girls. Of 416 cases seen by him and Dutton in the Congo almost 90 per cent were young adults (60 per cent males and 30 per cent females).

Macfie in South Nigeria among 222 cases found 63 per cent males and 37 per cent females. Among the adults the sexes were about equally divided, but no less than 67 per cent of the whole were under the age of sixteen, among whom the boys were twice as numerous as the girls.

Duration and Mortality.—In cases which have been followed up in sleeping-sickness camps the inevitable tendency is for cerebro-spinal symptoms to ensue sooner or later, when death usually occurs within three or four months, while the maximum duration of grave nervous symptoms is stated by Martin and Darre to be six to eight months and exceptionally a year. The earlier stages before nerve infection of the nervous system may last for a number of years, with latent periods of complete absence of fever which the same authors state last usually for six to eight months, but they have known them extend to four years and yet be followed by a fatal recurrence. In well-treated cases long intervals of health may be seen in European patients and some apparently complete cures have taken place, but great caution is required in stating that an individual case is cured, in view of the not infrequent relapses after several years.

MICROSCOPICAL EXAMINATION OF THE BLOOD, LYMPH AND CEREBRO-SPINAL FLUID

The Blood Changes, Presence of the Trypanosome.—As an account of the extremely uncharacteristic nature of the early stages of trypanosomiasis shows it to be impossible to diagnose the disease, with certainty, by purely clinical measures, the microscopical examination of the blood and tissues in which the trypanosome is to be found is of the greatest practical importance. Although the organism was first found in the peripheral blood, yet it may often be absent from it for considerable periods, and be very scanty and easily overlooked when it is present there. For this reason the examination of a small drop of fresh blood under a cover-glass with an $\frac{1}{8}$ -inch lens (which will allow of the active movement produced among the red corpuscles by the parasite being detected), although a method efficient when numerous organisms are present, often fails when they are very few. A much better way is to withdraw several cubic centimetres of blood from a vein, into a little citrate of soda solution, or several large drops from the finger tip, and centrifuge it in a small tube, the distal end of which has been drawn out into a narrower portion. Dutton and Todd advise slow centrifuging first for several minutes, and then for a shorter time at a higher speed. The thin layer of white corpuscles on top of the red should be pipetted off and examined fresh for the motile organisms, the whole procedure being completed as quickly as possible, on account of their rapid loss of motion outside the body. By this means the parasite can be frequently found in the blood when a simple microscopical examination fails to reveal it. The improved centrifuging method, however, has been to a large extent superseded by the simpler and still more efficacious mode of gland puncture to be described below. The microscopical appearance of the organism is shown in Plate 7. A drawing of the carrier of the infection, the tsetse fly, is also given. Dutton and Todd obtained positive results in 13·6 per cent by microscopical examinations of fresh cover-slip preparations of the blood, while by centrifuging 5 c.c. of blood

they found the trypanosome in 47 per cent, the proportion being about twice as high in advanced as in early cases. Gustave, Martin and Lebuff, also working in French Congo, obtained 38 per cent of positive results with direct blood examination and 92 per cent by centrifuging 10 c.c. of blood.

The Red Corpuscles and Haemoglobin have been carefully studied by Greig and Gray, who found them to be normal, in the early stages of sleeping sickness, while towards the end both might be actually increased without any signs of cyanosis.

The Leucocytes show marked changes, consisting of an increase of the mononuclears at the expense of the polynuclears, as in some other protozoal infections, while the total count is usually either within the normal limits, or shows a slight degree of leucocytosis. Table VII. has been worked out from a number of counts of Greig and Gray, while Dutton, Todd and Christy, in the Congo State, obtained very nearly similar results.

TABLE VII.—LEUCOCYTE COUNTS IN TRYPANOSOMIASIS AND SLEEPING SICKNESS

	Early Cases.	First Stage	Second Stage.	Total			
PART I. Total count :							
3000-6000 . . .				1 5			
6000-8000 . . .				7 22			
8000-10,000 . . .				6 25			
10,000-14,000 . . .				6 28			
14,000-20,000 . . .				4 15			
Over 20,000 . . .							
PART II. Differential count :—							
Percentage . . .	10-20	21-30	40	41-50	61-70	71-80	
Polynuclears . . .	3	24		24	3	0	103
Lymphocytes . . .	4	21		27	4	1	103
Percentage . . .	0 8	8-12	13-15	16 20	20-25	25	
Large mononuclears	22	26	18	16	12	9	103

It appears from this table that the total counts may vary greatly; the leucocytes are most frequently normal in the earliest stage, but a slight degree of leucocytosis is more common in the later ones. The increase of both varieties of mononuclears at the expense of the polynuclears is marked in all stages, and it is specially noteworthy that it is still evident during leucocytosis, although occasionally there may be some rise in the proportion of the polynuclears during a final terminal coccal infection very shortly before death, although without their being increased above the normal percentage.

The large mononuclears were within the normal limits in nearly one-fourth, especially in the early stages, while in 37 of the 103 counts they exceeded 15 per cent, so that the differential count affords no help in separating trypanosomiasis from malaria.

Cerebro-spinal Fluid.—The *Trypanosoma gambiense* was first found in sleeping sickness by Castellani while examining the cerebro-spinal fluid for the diplococcus, which he thought at the time was the cause of the disease, although it is now known to be but a very late and inconstant terminal infection. Bruce and Nabarro subsequently showed that, once the typical symptoms of sleeping sickness have set in, the organism can be always found in the cerebro-spinal fluid by centrifuging and microscoping the deposit, although it may be necessary to make more than one lumbar puncture before it is detected, as it may be periodically absent from this secretion as well as from the blood. The importance of this examination depends on the fact that once the organism has gained access to the central nervous lymph spaces the disease nearly always runs a more or less rapid course to a fatal termination, and the mental symptoms, which are so characteristic of the disease, are due to this extension of the habitat of the parasite, for they are absent as long as the trypanosome remains limited to the blood and the lymphatic glands. The organism is sometimes present in the spinal canal in such numbers as to be readily found by a simple examination of the freshly drawn fluid, but usually it is necessary to centrifuge in order to discover the organism. According to Christy, a temporary marked increase of the parasites in the cerebro-spinal fluid, without any rise in the number in the peripheral blood, may be accompanied by a marked rise in temperature. Dutton and Todd found trypanosomes in 13 per cent of early and in 96·6 per cent of advanced cases of sleeping sickness, while Martin and Lebeuf were successful in 70·17 per cent of 105 cases, including 83·33 per cent of clinically typical patients. Gray and Tulloch obtained 84 per cent of positive results by this method against 97 per cent by lymph-gland puncture and 52 per cent by blood examinations.

Lymphatic-Gland Puncture.—It has been known for a century that the earliest symptom of approaching sleeping sickness is a more or less general enlargement of the lymphatic glands, especially those in the posterior triangles of the neck. It was not, however, until Greig and Gray discovered that the *Trypanosoma gambiense* can easily and constantly be found in a small quantity of fluid withdrawn by puncturing such glands that their significance was fully realized. Owing to the rarity and inconstancy of the parasite in the peripheral blood, in all stages of trypanosomiasis and sleeping sickness, gland puncture is a greatly improved diagnostic measure, and allows of the detection of the trypanosome in the earliest stages of the primary uncomplicated disease, when there are commonly few if any clinical symptoms to draw attention to the serious infection which has taken place, and in a stage when treatment may have a considerable value in at least warding off or postponing the fatal extension to the nervous system.

For the purpose of this examination a small syringe with a tightly fitting piston is necessary, as good suction power is required. It is best to detach the needle before withdrawing it, so as to prevent the small amount of material within its lumen being dispersed into the barrel of the syringe. It is then diluted with a little citrated salt solution and examined fresh as soon as possible for the motile organism, another portion being stained if permanent specimens are desired. Greig and Gray obtained positive results by this method in 62 consecutive cases, while it is most successful in early ones, which are otherwise most difficult to diagnose. In advanced cases the glands may become indurated

and fibrous and shrink, when a puncture may be negative. Martin and Lebœuf were successful in 91.3 per cent by gland puncture, or slightly less than by centrifuging the blood, while in their hands even puncturing each group of enlarged glands gave 8 to 9 per cent of negative results, while it also fails in very early cases in which the glands are not yet puncturable. Dutton and Todd also found that out of 93 patients with much enlarged glands 89.3 per cent showed the parasites on puncture, and Todd has for long advocated gland palpation for the detection of early cases among travelling natives with a view to preventing their spreading the disease.

Diagnosis.—In the **early stage of uncomplicated trypanosomiasis** fever is the symptom which usually first brings the patient under observation. As the pyrexia is of an irregular intermittent character, malaria will probably be suspected, and must be excluded by the absence of malarial parasites from the blood and the failure of quinine rapidly to subdue the pyrexia. If a differential leucocyte count is made at the same time, the constant decrease of the polynuclears and increase of the proportion of the lymphocytes, and commonly also of the large mononuclears, especially if accompanied by a slight degree of leucocytosis, should, in the absence of malaria, lead to a suspicion of trypanosomiasis if the patient has resided in the endemic area of that disease. Enlargement of the superficial lymphatic glands should then be carefully sought for, and if a fairly general affection of them is found the suspicion will be greatly strengthened. One or more cubic centimetres of blood should be centrifuged, and the layer of white corpuscles above the red ones examined fresh with an $\frac{1}{8}$ -inch lens for active trypanosomes, the examination being repeated after a few days if negative at first. If none are found, one of the enlarged glands should be punctured, when the organism is almost certain to be detected if the disease be trypanosomiasis.

The Later Stage with Cerebro-spinal Involvement presents much more definite mental symptoms, which will direct attention to the nature of the disease, but here again a certain diagnosis in any but an advanced condition must depend on finding the trypanosome in the cerebro-spinal fluid by lumbar puncture which may have to be repeated before a positive result is obtained. In this stage the disease is said by G. C. Low occasionally to simulate locomotor ataxy.

TREATMENT

Thanks to the possibility of infecting animals with the organism of sleeping sickness and then testing various drugs on them, a number of remedies have been discovered which are of undoubtedly benefit in the disease. On the other hand, the absence of definite symptoms in the early stages and the chronicity of the affection, with a great tendency for relapses to occur after long intervals of absence of the parasite from the peripheral blood, necessitate much caution in drawing conclusions regarding the curative effect of any particular drug. Moreover, the stage of the disease exercises great influence on the effect of any treatment. In the late stage with definite symptoms of involvement of the cerebro-spinal system it is very rare for any treatment to have more than a slight retarding influence on the almost inevitable steady progress towards a fatal termination, as shown

by the extensive records of the camps in Uganda and other places. In the first stage with enlargement of the glands, but good general condition and complete absence of meningeal infection, as shown by the cell count of the cerebro-spinal fluid being normal or nearly so, the complete and prolonged disappearance of the parasites can usually be readily brought about in a majority of cases, and if this persists for two years and over, there is a good chance of its being permanent, although relapses have been occasionally recorded after considerably longer periods. This probability will be much enhanced if the precautions are taken of occasionally injecting the patient's blood into susceptible animals, and of examining his cerebro-spinal fluid obtained by lumbar puncture for increase of the cell count, negative results being important confirmatory evidence of the continued absence of infection. In the intermediate class of cases with more definite signs of the disease and distinct increase of the cerebro-spinal fluid cell count, but without clinical symptoms of involvement of the nervous system, the prognosis is much worse than in the first class of early cases, but considerably better than in the third class with confirmed nervous symptoms, as some of the second class have occasionally remained well for a number of years, although they are much more likely to relapse than those of the first class.

Another point of importance is the occurrence of **drug-fast** organisms, i.e. trypanosomes which have developed an especial degree of resistance to some particular drug, which then completely loses its power of causing them to disappear from the circulation. Fortunately in such cases a drug of a different class may prove efficacious in doing so. The possibility of developing such drug-fast organisms, which retain this property permanently when passed through a series of animals, has been proved experimentally, but fortunately it is not known to have occurred in the human subject. The occurrence of cases resisting some particular drug has led to the use of combinations of two or more chemicals belonging to different classes, such as the combination of atoxyl with mercury, antimony or one of the dyes which have trypanocidal properties. In judging the effect of any particular treatment the length of time the patients have been followed up after the cessation of the drug and the completeness of the observations and tests of his freedom from infection are of the greatest importance, as the longer the period of watching the larger will be the proportion of relapses and deaths, and the less the apparent efficiency of the treatment. In the following account of the action of different drugs these factors have been taken into account as far as possible.

The Arsenic Group of Drugs.—The majority of the drugs which have proved of real service belong to this group, **atoxyl** having been used most extensively and with the most lasting results. At first it was given in two large doses, and a number of instances of optic atrophy and blindness occurred, mostly in the hopeless third stage of the disease with involvement of the nervous system. By proper dosage this accident can nearly always be avoided, although Martin and Dacre have recorded a case after a total of 3 gm. had been given in a month, an amount which is usually well tolerated. **Soamin** is less toxic and closely related to atoxyl, and has been reported by Van Someren to have also given better results in Uganda, but the records of its use are less extensive than those relating to atoxyl itself. Manson has reported favourable results from atoxyl in a few Europeans, while Daniels recorded in 1915 a larger series of 29 cases, many followed up

for a number of years, and including 6 Rhodesian cases of the more severe form of the disease, all of whom died, while 7 more had been less than 2 years under observation, which is too short a time to enable the effect of the treatment to be safely judged. This leaves 16 cases, of whom 7 had died and 9 were in good health from $5\frac{1}{2}$ to 14 years after the commencement of the disease, so may fairly be looked on as cures. For a disease whose natural course is to end fatally in almost every case, these results in Europeans treated in an early stage of the disease are encouraging. In some of the cases other drugs were used to a certain extent as well as atoxyl, although the latter constituted the main treatment. The following are among the more important series of cases reported by other workers. Gamble in Portuguese Congo gave 4 grains of atoxyl daily subcutaneously up to a total of 100 grains, and out of 41 cases 19 were alive and working from $3\frac{1}{2}$ to 4 years later, so may be regarded as cured. Ouzilleau gave doses of 15 mg. per kilo every fifteenth day or even once a month, and examined his cases for parasites every month for a year, and reported that the majority were cured in that time. Moschet and Dubois in the Congo State gave .5 to 1 gm. doses weekly, and separately .1 gm. of tartar emetic intravenously for 4 to 6 months, and of 28 cases in the first stage 23 remained well for over a year, and some in the second stage were also cured. Ullrich in German East Africa used mainly atoxyl and reported 25 per cent of cures of two or more years' duration, while Raven in the Congo among 85 cases reported 56 as remaining well for from 12 to 18 months, 14 had died and 7 relapsed, the rest not being followed up. These results are also encouraging. On the other hand, Hearsay did not obtain even improvement in Nyassaland, where the deadly type of the disease due to *T. brucei* occurs, and Werner records a similar failure in this form.

Arsenophenylglycin has also been largely used with somewhat variable results. In German East Africa they were bad, and many deaths were reported as directly due to the drug. In Togoland Von der Helen found at least 40 mg. per kilo necessary to be effective, and in 233 cases in the early stage had 58 per cent discharged well after 9 to 35 months, and 12 per cent of relapses; while Le Fanu later reported from the same camp 77 per cent of cures. Raven in Togoland also found 40 mg. per kilo necessary, and both he and Aubert and Heckenroth report good results. In Uganda Hodges did not find this drug better than atoxyl and other drugs in use, but it was considerably less toxic. Hearsay in Nyassaland obtained no improvement with it in the deadly *T. brucei* type of the disease.

Salvarsan and **neosalvarsan** have also been extensively tried, .01 gm. per kilo being recommended as the dose of the former, and .013 of the latter. Von der Branden found a single dose caused the parasites to disappear from the blood for from 7 to 12 months as a rule, while salvarsan-copper in doses of .004 gm. per kilo was effective for from 19 to 24 months in 4 cases, and sodium salvarsan-copper in doses of .0053 for 8 to 12 months in 4 more cases. Relapses are eventually common, Aubert in 51 cases having 1 well for a year, while nearly all relapsed within 4 months. Bouret found that even repeated doses failed, while Ranken had 3 out of 7 remaining well after one year, and Kopke and Lutz also reported bad results. Le Fanu in Togoland, on the other hand, recorded 20 cases, with 19 recoveries with salvarsan, and 45 cases with 37 cures with neosalvarsan, or

82 per cent. The results are thus contradictory as regards ultimate effect, although nearly all observers are agreed that the immediate effects in causing the parasites to disappear from the blood are satisfactory. **Galyl** and **Iudyl** were tried in Senegal by Lafont and Dupont, who found doses of 5 to 10 eg. per kilo effective in clearing up the symptoms, including disappearance of enlarged lymphatic glands, and considered the results encouraging, although the cases had not been followed up long enough to ascertain the ultimate results. With **arasetin** Raven treated 35 cases, 23 of which were well 14 to 15 months later, while Mouchet and Dubois in 40 cases in the second and third stages used 1 gm. doses weekly for three or four doses with similar results to those obtained with atoxyl.

The above results indicate that the arsenic group supplies a choice of drugs of great value in the treatment of the first stage of trypanosomiasis, and to less extent in the second stage, but are of little use in the third stage of fully developed sleeping sickness. They also fail in the virulent Nyassaland type of the disease in all stages.

The Antimony Group of Drugs.—In 1908 Plummer and J. D. Thomson showed that sodium antimony tartrate caused the very rapid disappearance of trypanosomes from the blood of animals, and Cushny, Plummer, Thomson, Fry and Ranken investigated other similar compounds. In 1910 Kerandel treated himself for trypanosomiasis with series of four daily intravenous injections of tartar emetic in doses of 10 eg. with complete success after atoxyl had failed. Ranken in the Lado Enclave treated 76 cases of trypanosomiasis with 1 grain doses of finely divided metallic antimony intravenously for four days every five or six weeks with promising results. Later Simpson reported on cases treated in the same camp with metallic antimony in combination with other drugs, and recorded 53·8 per cent of recoveries with antimony and salvarsan, 69·5 per cent with antimony and atoxyl in cases in the first stage, and 38·3 per cent in the second stage of the disease. Kudicke reported good results from the use of sodium antimony tartrate intravenously, usually in combination with other drugs. Kerr reports a European case treated with soamin intramuscularly and soluble antimony salts intravenously who remained well two years later. Antimony oxide has been given intramuscularly without much success, abscesses often resulting. The soluble potassium and sodium antimony tartrates, however, appear to me to be worthy of much more extensive trial in trypanosomiasis, especially in view of their specific curative action in kala-azar, a disease which, before this treatment was employed, was almost as deadly as sleeping sickness.

Certain **aniline dyes**, more especially **trypanosan** and **trypaflavin**, have been a good deal used in combination with arsenical preparations, although not of much value by themselves. Perchloride of mercury was also advised in combination with atoxyl, but appears to have fallen out of use. Orpiment, arsenic trisulphide, can be given orally in 1 gm. doses on three successive days, and then once a week with some benefit, although less powerful than atoxyl.

AMERICAN TRYPANOSOMIASIS OR PARASITIC THYROIDISM OF CHAGAS

History.—In 1909 Chagas published a full account of a new form of human trypansomiasis discovered by him in the Minas Geraes State of Brazil. A biting insect, known locally as Barbeiro from its habit of attacking the face at night, was examined by him, and in its hind gut he found numerous Crinridia-like flagellates. Some of the large bugs were sent to Dr. Oswaldo Cruz, who caused them to bite a small Callithrix monkey, and twenty to thirty days after numerous trypanosomes of a new form were found in their blood. Chagas also transmitted the disease to guinea-pigs and other animals, and then set to work to discover the usual host of the new parasite; he eventually found it in the blood of a child, and infected a monkey and two guinea-pigs from the child's blood, reproducing in the animals the same trypanosome, and thus establishing the nature of the disease.

Geographical Distribution.—The infecting insect, now identified as a Triomata, is widely distributed in Central and South America, while our clinical knowledge of the new disease is less complete than the laboratory studies of its parasites, so the extent of its geographical distribution is probably very imperfectly worked out. Cases have been met with in the San Paulo Province of Brazil in addition to the State in which it was first found, but the coast-line is free according to Carini and Mociel. In Argentina and also in San Salvador in Central America infection of Triomata with the Trypanosoma cruzi, as the parasite has been named, has been met with, so the disease is likely to be found far beyond the confines of Brazil.

Etiology.—Trypanosoma cruzi differs from the African human forms in being found in large numbers in the blood of children suffering from the rare acute form of the disease, but not in that of the common chronic variety, although animals can usually be successfully infected by injecting them with 5 to 10 c.c. of such patients' blood. In these chronic cases, on the other hand, Leishmania-like forms are found in masses in the lungs, myocardium, striped-muscle cells, brain and spinal cord as shown by Gaspar Vianna in a fatal case in a child, while in artificially infected animals in addition they have been demonstrated in fatty and connective tissue, unstriped muscle of the intestines and arterial coats, the suprarenals, testicles, uterus and ovaries.

In the peripheral blood of man Chagas describes two forms. In one there is a large oval transversely-placed blepharoplast close to the posterior end, while the nucleus is oval or a longitudinally-placed long chromatin band, the anterior end is pointed, and the free portion of the flagellum of varying length. The other has a small round blepharoplast, a round nucleus and a broader body. After ingestion by the Triomata carriers the organisms become rounded and lose their flagella, and then multiply rapidly by division and later become pear-shaped and develop a flagellum again. After twenty-five hours they pass into the mid and hind gut of the insect, and become long flagellated forms with pointed ends. Eventually some of them may reach the salivary glands, although most appear to escape from the body in the faeces, and infection has been shown experimentally to be often of the contaminative type in animals, the infected excretions being rubbed

into the wound caused by the bite of the bug. The parasite is easily cultivated in the Novy-MacNeal medium, equal quantities of rabbit's heart blood and agar being advised by Chagas for this purpose. The fed bugs become infective from the eighth to the tenth day, and remain so for very long periods, probably for the life of the insects, which may exceed a year; including the larval and nymph forms, which may also carry the infection, it extends to two years. The insects which are most commonly found infected in nature are *T. megistus* and *T. sodida*, while in addition *T. infestus*, *T. chagasi*, *T. vivipara*, *T. dimidiata* and *T. geniculatum* have also been incriminated by various workers. Brumpt also obtained development of the parasite in the gut of bugs, especially *Cimex lenticularis*, and Blacklock confirmed this, but only once succeeded in producing the disease in an animal by their bites, although on injecting their intestinal contents animals could be infected, so he considers transmission by the bites of bugs must be very rare. Torres denies infection through bugs. The infection does not appear to be transmitted by heredity in insects.

The Triatoma megistus, first described under the name of *Conorrhinus megistus*, which is the commonest carrier of the disease, is a large insect more than an inch in length, the female being somewhat larger than the male. It lives in crevices in the walls of mud houses and out-buildings, such as coach-houses, stables, stores and hen-runs, where it lives on fowls' blood. It usually only attacks at night after the lights are out, the bite being almost painless. The young larvae are no bigger than bed-bugs, so can easily be conveyed in bedding, etc., but they as well as nymph stage can also convey the infection by their bites.

Prophylaxis consists in the construction of houses which will not harbour the carrier of the disease, and Chagas has recorded that by rebuilding the houses of other material than dry mud full of cracks, which harbour the *Triatoma*, the town of Bello Horizonte is now nearly free from the disease, although formerly termed "a nest of cretins."

Clinical Description.—The first account of the disease we also owe to Chagas, after whom it has been rightly named, while but little appears to have been added to his description. The **incidence** is nearly entirely among children, which excludes infection through water, probably few in poor families escaping in badly infected parts, including infants at the breast. Chagas divides the cases into acute, which are rather rare, and chronic, which are very common. The acute cases mostly occur in very young children, and run a course of from ten to thirty days with high continued fever sometimes rising to 40° C with slight morning remissions, and accompanied by puffiness of the face; hypertrophy of the thyroid gland even in children two or three months old; and a peculiar crepitant feel of the skin due to acute mucous infiltration of the subcutaneous tissues, and resembling that seen in myxoedema. General swelling of the lymphatic glands, especially those of the neck, axilla and groin, is a constant symptom. The liver is always enlarged, and the spleen usually is just felt below the ribs.

Post mortem are found serous effusions into the peritoneal, pleural and pericardial cavities and serous lepto-meningitis; enlarged fatty liver and hyperaemic spleen; marked

myocarditis with enlargement of the heart and sometimes haemorrhagic pericarditis; hypertrophy of the thyroid and of the lymphatic glands with general myxoedema of the subcutaneous tissues, and evident encephalo-meningitis with congestion and adherence of the meninges to the cerebral cortex.

The chronic form is divided by Chagas into five different types in accordance with the predominating affection of some particular organ or tissue. (1) A pseudo-myxoedematous form with enlargement of the thyroid gland, but only slight subcutaneous mucous infiltration and enlargement of the lymph glands, and sometimes of the parotid, together with cardiac insufficiency and tachycardia. It is seen in children up to fifteen, and may be complicated by corneal scars and repeated conjunctivitis. (2) The myxoedematous form with the characteristic features of that disease, including mental defect and complete arrest of development and abnormalities of the bones, and as a rule atrophy of the thyroid gland. (3) The cardiac form in which the myocardium is probably especially affected by the parasites, and showing disturbances of the heart rhythm. (4) The nervous form, showing numerous varieties of paralysis, aphasia or idiocy due to special incidence of the disease on the central nervous system. Among the most frequent symptoms are diplegia, spastic phenomena, chiefly affecting the lower extremities, athetosis, flexure contractions, usually accompanied by a greater or less degree of idiocy. (5) Chronic forms with acute or subacute exacerbations, often with fever, during which the trypanosomes may be demonstrated by successful inoculation of the blood into animals, such as guinea-pigs. The patients as a rule have great enlargement of the thyroid gland and the prognosis is bad. All classes of cases are found in houses infected with *Triatoma*, but not in the better-class residences, which are free from them.

The Blood was found by Dias to show a great excess of large lymphocytes (59 per cent. in one case) in the acute stage, while in chronic cases the proportion of both small and large lymphocytes was somewhat increased. The red count was normal.

The Urine shows evidence of slight hepatic deficiency. The **ovarian** functions in women were noted to be affected, with either excessive or deficient menstruation.

The Diagnosis is not always easy owing to the absence of trypanosomes from the blood on microscopical examination except in the rare acute cases. During febrile exacerbations it may often be established by injecting several c.c. of the patient's blood into guinea-pigs and watching for the appearance of the trypanosomes in their blood. The parasites are not sufficiently numerous in the muscles in the chronic form to allow of their being found by puncturing, while the organisms are not found in this way in the enlarged glands.

The Treatment consists in the intravenous injection of tartar emetic, which Gaspar Vianna first showed to be a specific in this form of human trypanosomiasis. Owing to the tender age of the patients and the frequent involvement of the heart muscle in the pathological process, great care should be exercised in using as small a dose as possible. The sodium antimonyl tartrate is probably preferable to the potassium salt, as I have found the former to be less toxic in kala-azar cases, for which these drugs are also a specific.

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III. ENTERIC FEVERS (TYPHOID AND PARATYPHOID)

EVER since typhoid fever was first clearly recognized in India by Scriven in 1854, its differentiation from other continued and remittent fevers in the East has been the subject of much discussion. Although well-marked cases, especially in fair-skinned Europeans, are straightforward enough, yet the milder types, without the characteristic rash or marked abdominal and intestinal symptoms, were commonly returned as "simple continued" or "remittent" fever: terms of the vaguest significance and hence readily adapted as a label for doubtful cases. Moreover, in the case of natives of India much doubt for long remained regarding the exact prevalence of typhoid, mainly because post-mortems were seldom obtained at the ages that we now know the disease is most frequent among them, while the subject was further obscured by the fact that as late as the 'eighties, eminent authorities, including J. F. P. McConnell, Physician and Pathologist at Calcutta, maintained that ulceration of the Peyer's patches might be found in cases of "remittent fever" other than typhoid.

With the advent of Widal's test these difficulties were largely cleared away, and the following references to the most important recent work will suffice to prove that typhoid fever is a common enough disease among natives—that is, the indigenous population of nearly every province of India.

Geographical Distribution of Typhoid among Natives in India.—In 1893 A. C. Crombie, I.M.S., maintained that natives of India were largely immune to typhoid, but his views were opposed by H. W. Pilgrim, W. J. Buchanan and others. In 1899 A. Buchanan recorded 25 cases of typhoid in natives in the Nagpur jail (Central Provinces) since 1894, with several post-mortems. In 1901 R. H. Elliot verified 13 cases by the serum test among natives in the General Hospital, Madras, within a period of three and a half months, and a month later G. Lamb recorded 7 cases with complete serum reactions in dilutions of from 1 in 10 to 1 in 50 in 6, and to 1 in 100 in the remaining one, and a second series in the following year of 10 cases, one of which reacted up to 1 in 100. In the same year the writer recorded 13 cases of typhoid in natives in the Medical College Hospital during five months, in 10 of which positive serum reactions in dilutions of from 1 in 100 to 1 in 500 were obtained, while one was also verified post mortem. Stokes reported the disease in natives of Abbottabad, on the Punjab frontier, and Duer from Rangoon, in Burma, in 1902, while A. Powell in 1904 recorded 24 cases in natives of Bombay. During the last six years I have verified the presence of typhoid by complete serum reactions in high dilutions in 50 natives in Calcutta and the neighbouring districts of Lower Bengal, but the disease appears to be less common in Eastern Bengal and Assam than in the western part of the province and other parts of India. With the exception of Eastern Bengal

and Assam, there is now reliable evidence of the frequency of typhoid in the indigenous population of every large province of India. It is worthy of note that the north-eastern areas, where the disease appears to be rare, are distinguished by the heavy and long-continued rainfall, frequent downpours commonly occurring during the hot-weather months of from April to the middle of June, when the typhoid areas are much dried up and extremely dusty.

In the native army the disease is much rarer than among European soldiers for the reason explained under the head of age incidence, but Gurkhas are especially liable to the disease, a fact which has been attributed to their semi-European meat-eating habits, but which may equally well depend on their being less exposed to the disease during early life in their Himalayan home than are the inhabitants of the plains of India.

The importance of the recognition of the wide prevalence of *typhoid among natives* in the East cannot be overestimated from the point of view of checking the terrible incidence of the disease among Europeans in such countries as India; for the strictest hygiene of the barracks will not entirely prevent the disease as long as the sanitation of the surrounding native population is neglected and the bazaars of the city are open to European soldiers, although E. Roberts is of the opinion that the infection is more frequently obtained in the cantonments themselves than in native bazaars. Native employees in regimental cook-houses have repeatedly been found to be sources of infection for European troops, carriers having been found among them.

In addition to their occurrence in British India the enteric group of fevers, including under that term the paratyphoids, are widely prevalent in tropical and sub-tropical countries. Thus, de Mello has found them to be common in Portuguese India. In the Dutch East Indies Snijders found the disease to be endemic, and Winckel found *B. typhosus* in 37 cases, and *B. paratyphosus A* in 10. In Ceylon Castellani found typhoid and both paratyphoid A and B, and a few cases due to a bacillus of the typhocoli group which he named *B. ceylonensis*. Gaide reported a number of cases in both Europeans and natives in Annam, and Gutierrez studied 125 cases in the Philippines, less than 10 per cent being in children under 15 years. F. Clark gives figures for Hongkong from 1898 to 1912, showing an incidence in Europeans of 3·52, in Chinese 0·08, and in other Asiatics of 1·30 per 1000. He found the risk of infection of Europeans to be eight times as great as in Surrey, England, and the chance of recovery slightly less. He states that a high proportion of Chinese deaths from enteric occur in children under 5 years, but not sufficient to support a theory of general typhoid infection in infancy.

In Egypt Phillips thinks typhoid is common in a mild form, differing in this view from Sandwith. In the Sudan Balfour considers typhoid is rare in natives, although a few cases occur in European troops. In British East Africa Johnson found typhoid to occur in Europeans chiefly in the dry, hot, dusty months of February and March, and to affect them nearly always during their first three years in the country, just as I found in India, while the disease is also reported from Portuguese East Africa. In South Africa Stock considers the disease to be common and to affect Kaffirs more than is usually thought, who may spread it. In Morocco Bernard recorded that in 1911 no less than 16·1 per cent of the French Army actually died of typhoid. In Algeria Sergent and Negre state that typhoid is endemic among the civil population, but inoculation was successful in protecting

the French soldiers living there. In the same town Boussel in 2½ years made 303 positive blood cultures, and found the typhoid bacillus 227 times and a paratyphoid 76 times. From a study of 10 years' records at Kingston in Jamaica Scott found a high prevalence, with a minimum in January and February and a maximum in June. In addition to culturing typhoid (24 times) and paratyphoid A (1 case) post mortem in cases with enteric lesions, he obtained them from the gall-bladder in 6 of 200 general autopsies, indicating the presence of carriers. In Cuba typhoid is also most prevalent in the summer months, affecting chiefly whites. Brown and Deeks found much typhoid in Panama, including many cases due to coli group organisms other than *B. typhosus*. The above references will suffice to show that the enteric group of fevers are found to be common in all warm countries in which they are looked for by competent observers.

PARATYPHOID

Frequency and Distribution.—In certain cases, clinically quite indistinguishable from comparatively mild typhoid, Eberth's *Bacillus typhosus* is not found, but instead very closely allied organisms intermediate between it and the *B. coli communis* can be cultivated from the blood in the early stages or the evacuations in the later ones. The two most commonly found are *B. paratyphosus A* and *B. paratyphosus B*, which have been closely studied, and are differentiated mainly by the sugar fermentation tests. In addition, further organisms of this group are met with, giving irregular or anomalous reactions, to some of which names have been given by various workers such as Castellani and Chalmers, but which have not yet met with general recognition. Unfortunately there is still great difference of opinion among bacteriologists regarding the value of minute differences in the sugar reactions, while organisms of this group may give anomalous reactions when first isolated, but after subculture for some time may revert to one of the well-known types. As clinically even the paratyphoids cannot be distinguished from true typhoid, these minute differences are of more academic than practical importance, so it will suffice to recognize the three common types of the *Enterica* genus of bacilli as the group has been conveniently named. The following table (Table VIII.) shows the proportion of the three organisms found by blood culture by a number of recent workers mostly in war hospitals. The subject of paratyphoid fever has become of great importance during the Great War on account of the phenomenal success of inoculation against the *B. typhosus* having nearly abolished that great scourge of armies in the field, but, as it does not protect against the two common forms of paratyphoid fever, these have become the predominant type of enteric, although happily they are now being reduced by the adoption of a mixed vaccine containing all three varieties of enteric bacilli.

All the figures in the table, except those of C. J. Martin and Upjohn, record the results of cultures from the blood, but their agglutination tests were most carefully carried out, and were in agreement with the blood cultures done in the same area, so have been included. It will be seen that in almost every case true typhoid was the least numerous class, while in all except Sarraihe and Clunet's tests *B. paratyphosus A* was much more frequently obtained, namely, in just over half the total cases, than *B. paratyphosus B*, although the latter predominated in the early part of the Dardanelles outbreak when the last-mentioned

observer's work was done, while an epidemic jaundice was prevalent at the time, which may account for the large number of anomalous bacilli they met with, which they called *B. paratyphosus D.*

TABLE VIII.

Place.	Workers.	Total Blood Cultures.	Positive Results.		B. typhosus.	B. paratyphosus A.	B. para-	Anomalous
			Negative Results.	Positive Results.			typhosus B.	Be-cult.
<i>Blood Cultures.</i>								
Paris	Coyon and Riatt	96	42	54	3	41	10	..
Heliopolis	Summons	178	128	50	3	35	12	..
Dardanelles	Archibald, Hadfield, Logan, and Campbell	147	21	70	41	15
Paris	Nobécourt and Peyre	375	223	152	23	79	40	..
Cario	Armitage	303	210	93	7	75	11	..
Dardanelles	Sarrahlé and Clunet	606	312	294	35	..	147	122 D
<i>Agglutination Tests.</i>								
Mudros	Martin and Upjohn	350	25	213	112	..
		Totals	117	513	373	..
						1003		
		Percentages of the three types	11.7	51.3	37.3	..

Among other noteworthy occurrences of paratyphoids the following may be mentioned. Paratyphoid A attacked 300 out of 1000 men of the United States Army on the Texas border, as recorded by Berry, high fever and much prostration resulting, but fortunately no deaths, probably due to the men having been inoculated against typhoid fever, but not against the paratyphoids. Paratyphoid A is also common in India, as shown by the following figures of the British Army since the paratyphoids were separately shown.

TABLE IX.

Year.	Paratyphoid A.		Paratyphoid B.		Total Paratyphoids.	
	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.
1911	103	2	1	..	104	2
1912	60	2	4	..	64	2
1913	79	2	79	2
1914
1915	78	..	6	..	84	..
1916	194	6	8	..	202	6
					533	12 2.25 %

The very great preponderance of paratyphoid A over paratyphoid B in India is well brought out by this table. Outbreaks of both forms of the disease have been traced to carriers. It is unnecessary further to consider the distribution of paratyphoids, as wherever true typhoid is common cases of paratyphoid have also been found by careful cultures from the blood or stools of typhoid-like fevers.

The Incidence of Typhoid among Europeans in India.—Since the days of Bryden the special incidence of typhoid fever in India on young European soldiers during their first few years' service in India has been well known. Opportunities are less favourable for studying this point in the case of civilian Europeans in the tropics, but during the last six years I have carried out the Widal test in nearly all fevers which could possibly have been typhoid in the large European hospital at Calcutta, an analysis of which has furnished the following results. Two different classes of patients are included among the typhoid cases, requiring separate consideration. Firstly, there are the European civilian immigrants, who nearly all go to the tropics in early adult life, and secondly, there are the Europeans of pure and mixed blood, who have been born and bred in India, nearly all of whom belong to the poorer classes and for the most part live in parts of Calcutta which are also inhabited by the indigenous Indians.

Table X. shows the incidence of typhoid among immigrant Europeans in Calcutta classed both according to their age and sex and the length of their residence in India.

TABLE X.—THE INCIDENCE OF TYPHOID AMONG 125 EUROPEAN IMMIGRANTS TO INDIA

Age.		Under 15.	15-20	21-25	26-30	31-40	40	Total	Percent- age.
Under 1 year in India	(Males .	0	9	12	18	11	3	63	52.8
	(Females .	0	0	0	3	0	0	3	
1-2 years in India	(Males .	0	0	5	4	1	0	10	11.2
	(Females .	1	0	1	0	2	0	4	
2-3 years in India	(Males .	0	1	3	6	4	0	14	11.2
	(Females .	0	0	0	0	0	0	0	
Over 3 years in India	(Males .	1	1	5	6	8	7	28	24.8
	(Females .	0	0	0	1	2	0	3	
Total	(Males .	1	11	25	34	24	10	115	
	(Females .	1	0	1	4	4	0	10	

These figures require little comment as they show a similar incidence among these civilian Europeans to that of their military brethren. The only child attacked had been ten years in the country, while one lad of nineteen had immigrated thirteen years before his attack. Out of 125 patients no less than 75 per cent were attacked within three years of reaching India, and as many as 53 per cent contracted typhoid within one year of their arrival in Bengal, and 64 per cent within the first two years of their residence in the tropics. A

few sailors developing the disease within two weeks of their arrival in port have been excluded, while the figures remain practically unchanged if all sailors are omitted.

The importance of this fact lies in the certainty that this heavy incidence of typhoid during the first few years of residence of all classes of European immigrants in the tropics being prevented to a large extent by the more general adoption of Wright's prophylactic inoculation, now the favourable results of this procedure have been confirmed by very extensive experience (see p. 99).

Age Incidence of Typhoid among Indian-born Europeans compared with that of Temperate Climates.—When we come to consider the incidence of typhoid on the class of Indian-born-and-bred Europeans we meet with the very striking results shown in Table XI. In the first place the cases are divided more equally between the two sexes (instead

TABLE XI. AGE INCIDENCE OF TYPHOID IN INDIAN-BORN EUROPEANS
COMPARED WITH THAT OF TEMPERATE CLIMATES

Age.	Under 40								Over 40	Total	Per cent. age
	11	11-14	15	20	25	25-30	30-40	40			
Born in India	Males	23	8	23	11	2	8	1	76	57·14	
	Females	11	15	13	9	1	4	1	57	42·86	
Total		34	23	36	20	6	12	2	133		
		57		56		20					
Percentage		42·86		32·10		15·04					
Curschmann's Hamburg cases		11·02		58·68		30·30					
Curschmann's Leipzig cases		9·59		49·40		40·01					
Osler's Montreal cases		7·73		46·69		45·58					

of a marked preponderance among the males of the immigrant classes on account of their far exceeding in numbers the females). Secondly, the age incidence of the disease differs very widely from that of temperate climates of Europe and America, as illustrated by the figures of Curschmann and Osler, which are given in the table. Thus in the Calcutta series 42·86 per cent of the patients were under 15 years of age, against from 8 to 11 per cent in temperate climates, and in correlation with this only 15·04 of the tropical cases patients were over 25 years of age, against 40 to 45 per cent in Europe and North America. In the intermediate periods of life between 15 and 25 years of age the incidence is nearly the same in both climates. *The incidence, then, of typhoid among Europeans born and bred in the tropics is four times as great among children under 15 and nearly three times as little among adults over 25 years of age, as compared with temperate climates.*

It has been mentioned that this class of Europeans live intimately mingled with the native Indian population, and under sanitary conditions little, if at all, superior to those of the better-to-do Indians. It has for long been suspected that the relative infrequency

of typhoid among adult Indians, as compared with that of immigrant Europeans in the tropics, might be due to many Indians having suffered from the disease in childhood, but it has been very difficult to obtain clear evidence on this point, as native children are very rarely brought for admission to hospital when suffering from fever. The disease is, however, common among native Christian children in the hands of European missionaries, who are readily brought to hospital; indeed, during the last few years I have repeatedly obtained positive serum tests for typhoid in high dilutions of 1 in 100 or more with the blood of Indian children, often the children of Indian medical men. There appears, then, good reason for believing that the remarkably low age incidence of typhoid among Indian-born Europeans also applies to the indigenous population among whom they live, and thus the comparative rarity of typhoid among the large adult population of the Indian Army and jails is explained without supposing that typhoid is a very rare disease among the natives of India, as held by E. Roberts in his recent book on enteric fever. The fact that, in every city provided with large hospitals with special physicians and medical wards, typhoid has been found to be quite common among the native population is too striking to admit of the disease being considered to be rare among Indians because such patients have not been very frequently admitted to the district dispensaries, which are mainly occupied with surgical cases.

SEASONAL INCIDENCE OF TYPHOID IN INDIA

This has been carefully studied by E. Roberts, from whose work on enteric fever in India, Table XII., showing the percentage of cases in each quarter of the year from 1895 to 1898 in different Army Commands, has been taken.

TABLE XII.—SEASONAL INCIDENCE OF TYPHOID IN INDIA (E. ROBERTS)

	First Quarter.	Second Quarter.	Third Quarter.	Fourth Quarter.
Bengal . . .	23.5	34.0	19.8	22.7
Punjab . . .	10.2	42.9	24.9	22.0
Madras . . .	22.4	21.0	36.4	20.0
Bombay . . .	13.2	22.0	43.3	21.5
INDIA . . .	18.1	31.3	28.1	22.4

This shows a maximum in the dry hot months in Bengal and the Punjab, but in the wet monsoon months in Bombay. Roberts describes three rises and falls in the Punjab and Bengal commands, with their maxima in April and May, July to September, and in November respectively; but they are affected by movements of troops and other factors.

In Calcutta the majority of cases occur in Europeans in the dry, cold and hot seasons, falling to a lower point in the rains. In some years, however, numerous cases are also seen in Europeans during the rainy season. On the other hand, among natives over half

of my cases occurred in the four wet monsoon months from July to October. The probable explanation of the difference is that in Europeans, who do not drink unboiled or unfiltered water, the infection is mainly through dust in the dry seasons; but in natives infection is often through water, which is specially liable to be contaminated in the wet months with rising ground water level and frequent opportunities for surface filth being carried into tanks and other collections of water.

ETIOLOGY AND PROPHYLAXIS

Our knowledge regarding the ways in which the typhoid bacillus gains access to the human body has made remarkable advances in recent years. That the infection is sometimes water-borne, causing explosive outbreaks with large numbers of cases, as in the Maidstone epidemic, is certain. Far more frequently the bacillus is conveyed from the stool or urine of an infected person either through the agency of flies or directly to food from a "carrier" of the disease; that is, by an apparently healthy person who has suffered from a previous attack of typhoid, occasionally of such a mild nature as to be overlooked, and who continues to excrete typhoid bacilli, usually in his stools, for an indefinite period after his recovery from the febrile attack, the period having been known to extend to as long as 29 years. Such unfortunate persons are a grave danger to the community, as in a case reported by Dudley in which a man, who suffered from enteric fever in 1898, and was found to be a carrier in 1914, during which time no less than 53 cases of the disease occurred on the ships on which he served. The most dangerous class of carriers are those employed in connexion with human food, as in the case of a cook reported by Sacquepee and Bellet who infected 19 persons out of 250. The discovery and removal from dangerous positions of these carriers constitute a most important part of the prophylaxis against the disease, and much was done in this way in Germany at a comparatively early date, at the instance of Koch, and after an investigation in India by Greig (1906-1908) the system was introduced in connexion with the British Army in India with important practical results. Depots were formed in charge of competent bacteriologists in different parts of India, to which all convalescents from enteric fevers, including paratyphoids, were sent, and examinations of their stools and urine were made at regular intervals during a period of three to six months, and only after repeated negative results had been obtained, to exclude intermittent excretion of the dangerous bacilli, were they allowed to return to their regiments or corps. D. Harvey, who continued the work in India from 1908 to 1911, arrived at the conclusion that "all cases of enteric fever (including under that term the paratyphoid fevers) in military service are caused by contact with infected persons, either direct or indirect." The observations showed that out of 86 men 10 or 11·6 per cent of typhoid convalescents passed typhoid bacilli for over six months after defervescence of the fever, although only 2 developed into true chronic or permanent carriers. These figures clearly show the importance of isolating typhoid convalescents until they are proved to be no longer excreting enteric bacilli. In true carriers the gall-bladder is permanently infected, and all treatment with intestinal antisepsics, such as urotropine and hexamine, usually fail to cure them, while vaccine treatment only succeeds in a certain number of cases, so they form a most difficult problem.

One thing is certain, namely, that they should be rigidly excluded from employment in connexion with preparing human food, and from remaining in the army, as ordinary sanitary measures, although they have done much to reduce typhoid, fail adequately to deal with the carrier.

Protective Inoculation against Typhoid Fever.—In Haffkine's method of inoculation against cholera, cultures of the living comma bacillus were injected subcutaneously. Such a procedure was clearly unjustifiable in the case of the organism of typhoid, which is disseminated through the body by the blood stream. Sir A. E. Wright, however, showed by a long series of experiments that the bactericidal power of the blood against the typhoid bacillus can be greatly increased by the subcutaneous injection of cultures, which have been killed at a temperature of 60° C. for one hour, a method which has now been extensively used as a prophylactic measure, especially among soldiers going to the tropics, or under conditions where typhoid is unusually prevalent, such as South Africa during the Boer War. Great difficulties were met with in obtaining accurate data of the results of this method, but several Committees have now reported in favour of its protective value, the last, that of the Royal College of Physicians of London, concluding: "After careful scrutiny of the statistics from both official and private sources, which have been made available, we are of the opinion that not only is a lessened susceptibility to the disease brought about as a result of the inoculations, but that the case mortality is largely reduced." Sir A. E. Wright has critically examined all the data then available in his book on the subject, and sums up as follows: "With two slight exceptions, the incidence of typhoid was decreased by at least half, and reached from a six-fold to a twenty-eight-fold reduction in some instances. Further, the case mortality was rather less than one-half, aggregating 8·0 per cent among 1758 inoculated persons attacked, and 16·6 per cent in 10,980 uninoculated under the same conditions." The total effect was, thus, rarely less than a four-fold reduction in the death-rate of those subjected to this prophylactic measure, in spite of the conditions of its trial being frequently far from ideal.

As a result of recent researches, carried out at the Royal Army Medical College laboratories by Leishman, a typhoid vaccine of uniform strength and efficiency was made, which produces a minimum degree of fever and very slight symptoms, but which furnished remarkably good results in the case of an outbreak of typhoid in the 17th Lancers shortly after the regiment reached India. Out of a total number of 593 men, 127 were inoculated twice, 23 more once only, while 443 were uninoculated. Out of 63 cases of typhoid 61 were among the uninoculated, and the remaining 2 in those who refused the second dose, none who had the double inoculation being attacked. There is also evidence to show that the protection afforded lasts for two years, after which it is advisable to repeat the inoculation.

Taking the convincing evidence of the protective action of the vaccine, together with the fact I have shown on page 94, namely, that 75 per cent of the cases of typhoid among European immigrants in Calcutta occurred within the first three years of residence in the tropics, I have for long advised every one going to parts of the East where typhoid is common to submit to the double inoculation. The effect of the vaccine now used is only a few hours' fever and slight malaise for a day or two, a small price indeed to pay for

ENTERIC FEVERS

the very considerable protection afforded against the greatest scourge of Europeans in the tropics.

The most conclusive evidence of the protective value in inoculation is afforded by the extensive and accurate figures of the British Army in India and other military forces, as shown in the following table :

TABLE XIII.

Years.	Rates per 1000.				Rates per 1000.			
	Inoculated.			Cases	Unmocculated.			
	Cases	Deaths	%		Deaths	%		
British Army in India, 1911	1.72	..	10.37	5.9	..	17.18		
" " 1912	1.2	15	12.8	5.6	..	40.0		
" " 1913	0.9	12	..	5.3	1.76	..		
Japanese Army, 1908-1912	0.7	10	..	5.0	0.8	..		
Italian Navy, 1907-1910-1916	0.91	3.72-4.52		

In the case of the British Army in India figures given in the table, the paratyphoid cases were excluded as far as possible, which gives the best test, because conclusive evidence has accumulated to show that inoculation with the *B. typhosus* does not protect appreciably against the incidence of the paratyphoids. The figures for the British Army in France during the war up to November 1, 1916, showed 1684 cases of typhoid, and 2534 cases of paratyphoid fever, and 353 of an indefinite type, which presents a wonderful contrast to the 60,000 cases which occurred in a far smaller force during the South African War. It must be remembered that inoculation is still voluntary in the British Army, although the men know its worth so well that since 1913 in India over 93 per cent of the British troops have been inoculated.

The use of a triple vaccine, T.A.B., containing *B. typhosus* and *B. paratyphosus A* and *B.*, which was used for several years by Castellani in Ceylon, is now being used extensively in the British, French and American armies, and there are already indications that the number of paratyphoid fevers are being reduced by this measure. Castellani showed, and others have confirmed his observations, that the triple vaccine does produce antibodies against all three varieties of enteric bacilli, and that, too, with very little more distress and reaction than after the original typhoid vaccine. He advises 500 million *B. typhosus* and 250 million each of the paratyphoids per c.c., 0.6 c.c. for the first dose and 1.2 for the second. Sergent in Algeria advises a vaccine made by Vincent's method, containing 400 million typhoid and 200 million of each paratyphoid organism, four injections being given, totalling 3300 dead bacilli. Widal and Salimbeni reduced the number of doses to two, using a vaccine containing 10,000 bacilli in 3 c.c. killed at 56° to 57° C., the first dose being 1 c.c. and the second 2 c.c. after a week. Later still they recommended only one dose containing 6000 million in 1 c.c., although most workers consider it much better to give two doses with a week or ten days' interval. Coppinger and Gibson found the reaction began earlier with the triple vaccine, and that the agglutination test after it

shows but little evidence of the production of antibodies against the paratyphosus A, which is a most important one in the army.

The value of a combination of the above two chief prophylactic measures against typhoid, namely, inoculation, and the elimination of carriers, is well shown in the steady diminution of typhoid in the British Army in India, especially since both were extensively used from 1909, when the two enteric depots were in full working order, as shown in the following table (Table XIV.). It is only since 1911 that separate figures of the paratyphoid cases are available, as shown in the table under that heading, and in order that the figures of the different years may be strictly comparable the following data include all three forms of enteric, although up to 1916 the vaccine only contained B. typhosus, which does not protect against the paratyphoids, which have recently been as numerous as the typhoids, but for which the reduction would have doubtless been even greater.

TABLE XIV.

	Total Enteric Cases Percentage inoculated.	Rate per 1000	Total Deaths.	Deaths per 1000
1902	1012	16.7	260	4.29
1903	1384	19.6	295	4.19
1904	1395	19.6	267	3.76
1905 ¹	1146	16.1	213	2.99
1906	1095	15.6	224	3.19
1907 ²	910	13.1	192	2.77
1908 ³	1001	14.5	190	2.76
1909 ⁴	639	8.9	113	1.58
1910	66	4.6	46	.63
1911	85	3.8	24	.33
1912	90	2.6	28	.39
1913	93	2.3	18	.25
1914	93	2.9	13	.21
1915	93	3.7	16	.36
1916	93	5.2	23	.54

In 1905 inoculation of drafts of men in India was commenced.

The recommendations of a Committee appointed in 1906 began to operate in 1907. The principal measures advised were (*a*) convalescent enterics to be isolated in the hill depots with facilities for bacteriological examinations; all British or native employees in kitchens, bakeries, messes, dairies and mineral-water factories, etc., to be examined to detect and exclude all typhoid carriers. Nursing orderlies to be inoculated against enteric, and specially trained in disinfecting measures, etc., and convalescent soldiers to be no longer employed in nursing enteric patients.

In 1908 the Nami Tal convalescent depot for enterics was opened.

* In 1909 the Wellington convalescent depot was opened for the south of India cases and inoculation in effective amount introduced.

The increase in 1916 appears to have been mainly due to an outbreak of paratyphoid A in Bangalore, where two carriers were detected. Nearly two-thirds of this year's cases were paratyphoid, against which the men were not inoculated, but this measure has now been commenced.

CLINICAL DESCRIPTION OF TYPHOID IN INDIA BASED ON AN ANALYSIS OF THE NOTES OF FIVE YEARS' CASES VERIFIED BY SERUM TESTS IN THE CALCUTTA HOSPITALS.

Owing to the great difficulty in the accurate clinical differentiation between the milder forms of typhoid and other fevers met with in the tropics, it is essential that any description of the disease in the East should be based on a considerable series of cases verified by efficient serum tests. The following account is founded on an analysis of the notes and four-hourly temperature charts of over 100 cases of typhoid treated in the Calcutta European Hospital during the last six years, about 90 per cent of which were verified by the serum test, while the remainder were absolutely typical clinically, and have been included because among them were several very severe fatal cases, the omission of which would have involved errors regarding the death-rate and other important points. A further series of 135 cases were subsequently analysed, making a total of 264, and yielded figures closely parallel with those in the tables of the first edition of this work. The additional figures have been added to the most important of the following tables, except when they were found to make no appreciable difference. They will therefore suffice to allow of an analysis of the more important features of the disease in comparison with the accounts of European and American writers, and a study of the differentiation of typhoid from other tropical fevers.

THE GENERAL COURSE OF THE DISEASE

Typhoid in the tropics is in its essential features very similar to typhoid of temperate climates, with the exception that it shows greater severity and longer duration, while the pyrexial curve somewhat less frequently shows the classical course described by European writers, especially as regards its rise.

The Duration of the Fever.—In temperate climates there are few fevers running a course of three weeks or more with which typhoid is liable to be confused, but the case is very different in the tropics, so that a knowledge of the limitations of the duration of typhoid fever in hot climates is of great importance. Table XV. gives the data on this point of my Calcutta series, arranged so as to be comparable with Curschmann's European figures.

TABLE XV.—DURATION OF TYPHOID FEVER IN THE TROPICS

	- 15 Days.			15-21 Days.			22-33 Days.			Over 33 Days.			Total.		
	Recovered.	Died.	Total	Recovered.	Died.	Total	Recovered.	Died.	Total	Recovered.	Died.	Total	Recovered.	Died.	Total
Adults over 15 . . .	4	2	6	23	8	31	32	6	38	22	3	25	81	19	100
Percentage . . .				37			38			25					
Children under 15 . . .	2	..	2	7	..	7	13	1	14	5	1	6	17	2	29
Percentage . . .				31			48.2			20.8					
Total cases . . .	6	2	8	30	8	38	45	7	52	27	4	31	108	21	129
Percentage (4.7) . . .				35.7			40.3			20			16.3		

Curschmann's Figures :

Adults up to 55 . . .	50.5			29.3			14								
Children to 14 . . .	76.5 ¹			16.0			7.5								

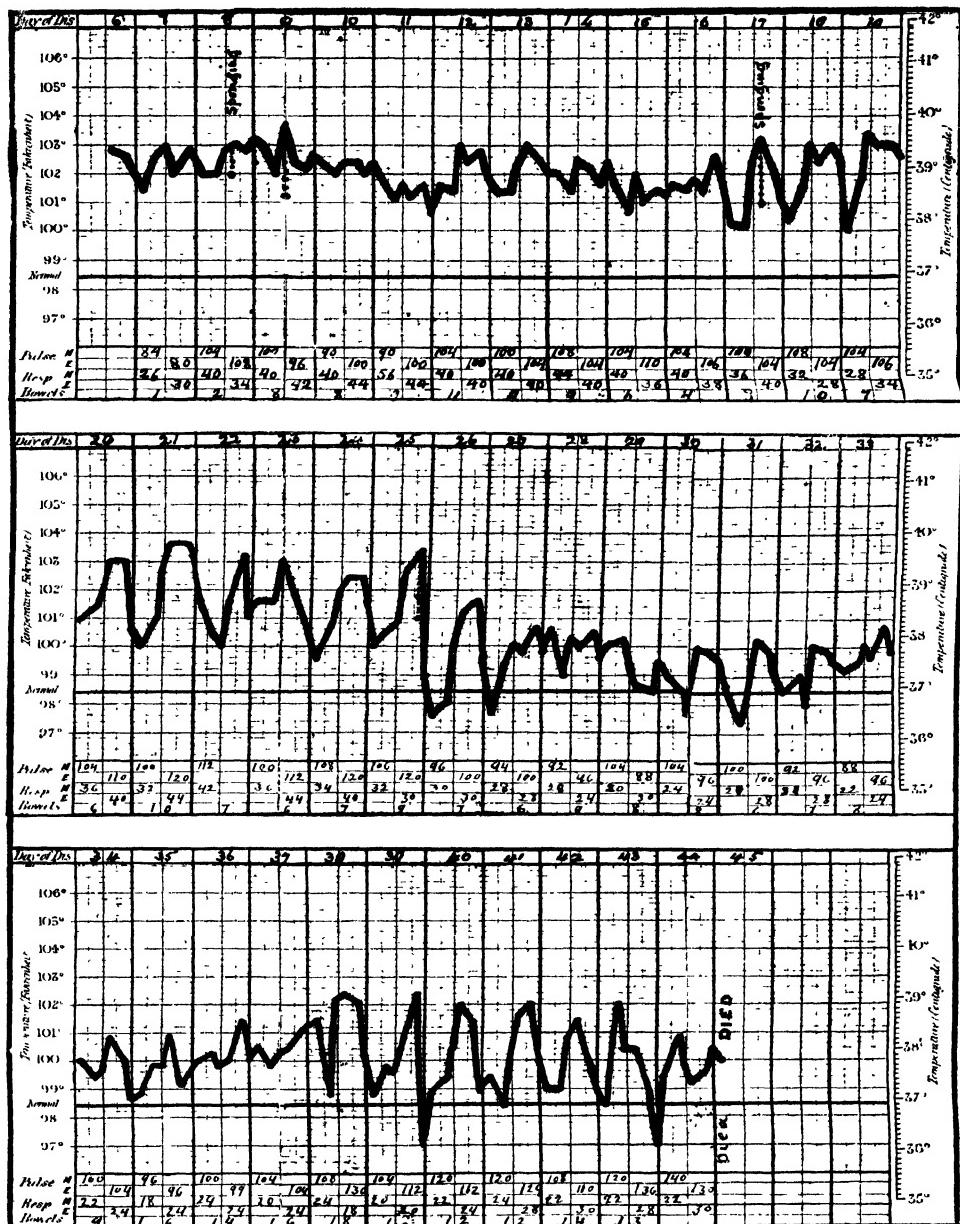
¹ Curschmann gives this figure as 88.5 per cent, which appears to be a misprint.

The cases of not more than three weeks' duration have been subdivided to show the number of less than fifteen days' fever, as such abortive cases are particularly liable to be overlooked in the tropics. Excluding 2 cases which were fatal, they form, however, only 4.7 per cent of the whole, so that they are quite uncommon.

The main point brought out by this table is the larger proportion with prolonged fever in typhoid in the tropical East as compared with that of temperate parts of Europe. This is the case with both adults and children, the divergence from the European standard being most marked among the latter. Thus, in only about one-third of the Calcutta cases did the fever terminate by the end of the third week, against from one-half to three-quarters in Curschmann's series, while in 25 per cent of the adults and 20 per cent of the children the duration of the pyrexia exceeded thirty-three days, against 14 and 7.5 per cent respectively in Germany. These differences appear to be too great to be due solely to the comparatively small number of my cases, so we can conclude that the temperature curve of typhoid runs a longer course on the average in tropical India than in temperate climates. This difference does not appear altogether strange when we take into account that during seven months of the year in Calcutta the mean temperature of the air is about 80° F. or over. Chart 12 shows a prolonged case terminating fatally on the forty-fifth day.

The Course and Type of the Temperature Curve.—For purposes of description the temperature curve of a typical case of typhoid fever has been divided up by Curschmann into the following stages. The step-like rise, lasting usually three to five days, but sometimes extending to seven; the fastigium, or continued stage of high fever at about 103° to 104° F., with but slight diurnal variations within the limits of those of the normal

CHART 12 (Case 992)

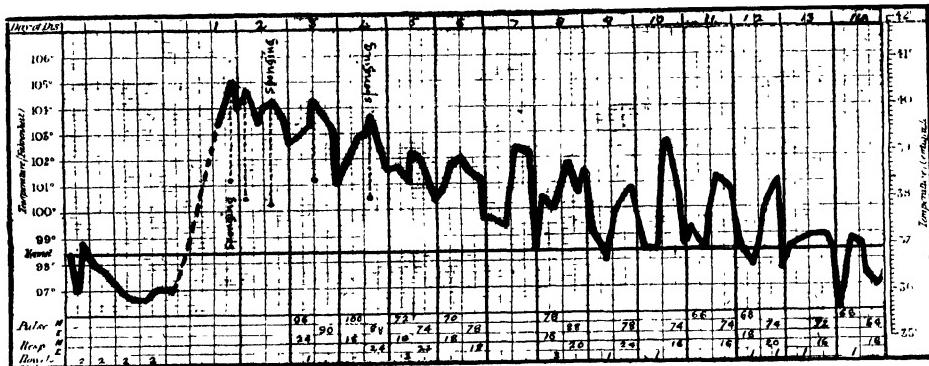


Prolonged typhoid, showing typical high continued type in early stages passing through remittent to the intermittent form, and terminating fatally on the forty-fifth day with haemorrhage.

temperature, and varying widely in its duration from a few days to three or four weeks ; and the final stage of steep curves by which the temperature gradually declines once more to the normal and not infrequently passes into a subnormal stage during the early period of convalescence. This classical course is very far from being constant even in temperate climates, where wide departures from it are seen, while in the tropics it is the exception rather than the rule to meet with such a typical case. A study of these variations is of very great importance in the differentiation of typhoid from other tropical fevers, for I believe that the course of the temperature, when rightly considered, is of the greatest diagnostic value, and will allow of an early recognition of a large proportion of cases, as will appear from the following analysis of my Calcutta series.

The Period of Rising Temperature.—This stage, especially, differs in India from the classical step-like rise. Only a few cases came under observation during the earliest period of the disease, but out of 6 cases admitted during the first two days of fever none showed a gradual rise of temperature, but in each it had already risen to from 103° to 105° F. Chart 13 illustrates the rapidity with which the pyrexia may reach a high degree,

CHART 13 (Case 882)



A short typhoid with abrupt initial rise of temperature to 105° on the first day. Note the slow pulse.
Widal positive to 1 in 100 on eleventh day.

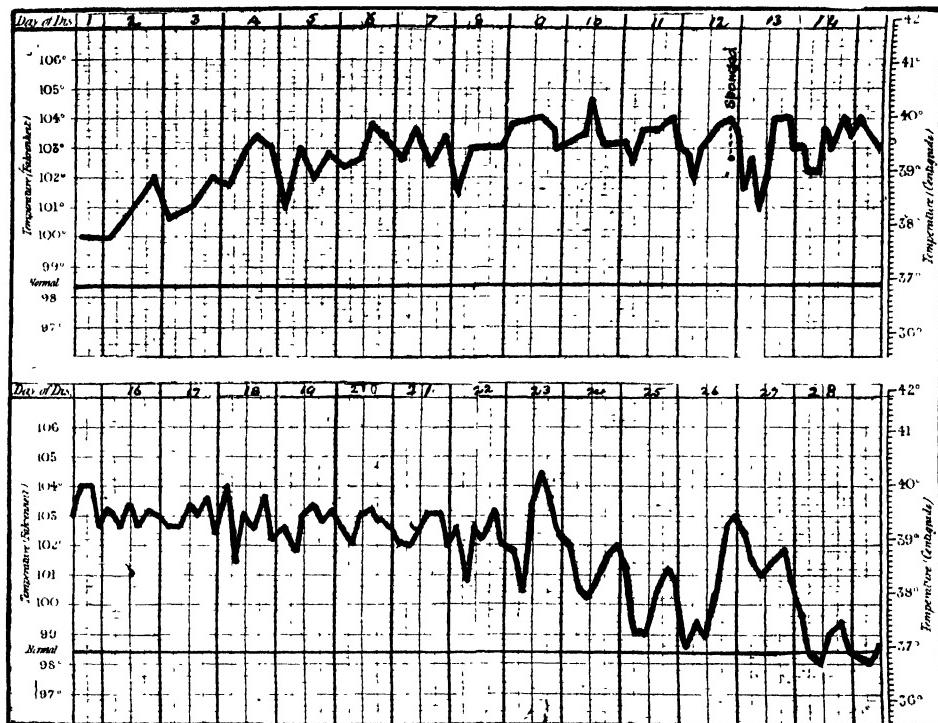
for the patient had been in hospital for the treatment of a venereal bubo, with a normal temperature for ten days up to one day before his readmission for typhoid fever with a temperature of 103.4° , which rose further to 105° four hours later, but ran a short and mild course with a positive Widal reaction up to 1 in 100 dilution. He gave a history of a rigor three hours before his second admission for typhoid.

On the other hand, Chart 14 shows the typical step-like rise at the beginning of typhoid, although it is almost the only one in my collection. The patient was admitted on the seventeenth day of his fever, but brought the earlier records of his temperature with him.

Turning to the histories obtained of the onset of the disease we find the same tendency to a sudden onset of the pyrexia. Thus out of the last 58 cases in which the history was carefully recorded, in no less than 30 a sudden onset was noted, in 23 of which rigors were

said to have preceded the rise of temperature. In the whole series in 32 per cent a sudden onset was recorded, in 42 per cent it was gradual, and the remaining cases were doubtful. In some further inquiry showed that the fever commenced with chilliness rather than an actual rigor, but this is also often the case in many fevers in the tropics, including malarial ones. The frequency of this sudden onset of the fever of typhoid in the tropics should be borne in mind as it may increase the difficulty of diagnosis in the early stages. In many cases, however, a typical history of gradual onset of the fever, preceded by headache and

CHART 14 (Case 994)



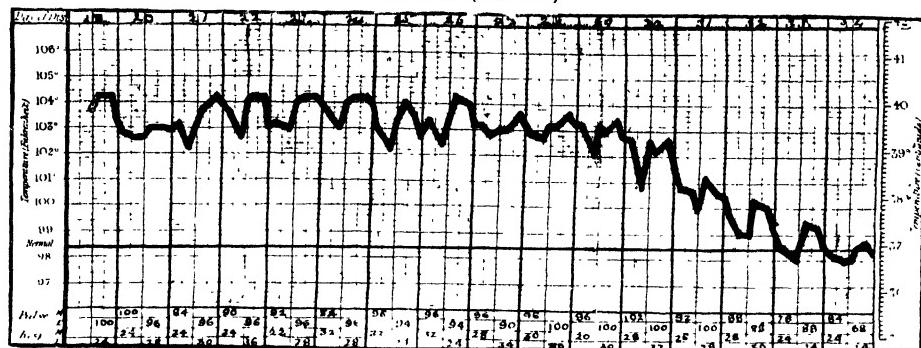
Typical typhoid with step-like rise, high continued pyrexia and remittent fall.

Tassitude was obtained, and may be of material assistance in the diagnosis of typhoid from malaria and seven-day fever, both of which almost always begin suddenly.

The Stage of Continued Fever.—Although the rise of temperature is so often atypical in the tropics, the period of high continued fever is usually quite characteristic and of great diagnostic value. By "high continued fever" I mean a temperature keeping persistently above 101° F. (apart from temporary falls for an hour or two brought about by the application of cold or powerful depressing antipyretic drugs such as antipyrin) and not varying over more than 2° F. for at least forty-eight hours, a four-hourly temperature

chart being kept. Thus it may vary between 101° and 103° or from 102° to 104° , or between intermediate points, but the diurnal variations do not range beyond 2° in the typical curve which I designate by the above term, and which is well illustrated by Chart 15 from the tenth to the nineteenth day of the disease. The importance of this definition

CHART 15 (Case 907)



Typhoid showing typical high continued pyrexia and slow pulse.

is that I find this high continued type of fever is very common in typhoid, while it is rare in any other fever in the tropics which is liable to be mistaken for typhoid. The last qualification is necessary to exclude such diseases as uncomplicated lobar pneumonia, and the later characteristic stages of kala-azar, in which a similar type may occur, but these are usually readily differentiated from typhoid by other symptoms.

TABLE XVI. THE FREQUENCY OF DIFFERENT TYPES OF TEMPERATURE CURVE IN TYPHOID

	Adults.				Children.				Total Cases.		
	High Continued.	Romantic	Low Continued.	Inter- mittent.	High Continued.	Romantic	Low Continued.	Inter- mittent.	High Continued.	Other Types.	Total
Admitted first ten days	Cases	55	12	1	2	22	4	—	77	21	98
	Percentage	78.6	17.2	1.4	2.9	78.6	14.3	—	78.6	21.4	
Admitted after tenth day	Cases	11	10	..	1	2	4	..	13	15	28
	Percentage	50.0	45.5	..	4.5	33.3	66.6	..	46.4	53.6	
Total cases	Cases	66	22	1	3	24	8	2	90	36	126
	Percentage	68.7	23.9	1.1	3.3	70.6	23.5	5.9	71.4	28.6	

Table XVI. has been prepared to illustrate the frequency with which this high continued type of fever was met with in my typhoid series in cases admitted at different periods of the disease, for it is specially common in the difficult early stages, but more often absent

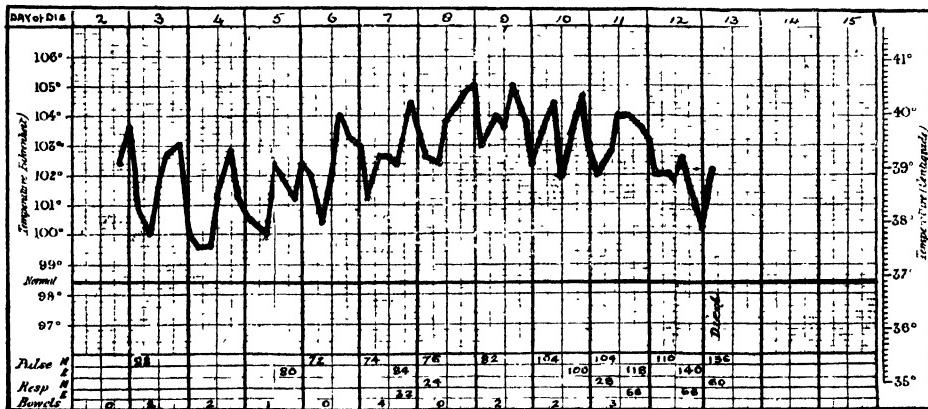
in the later ones when the temperature is declining. The age has also been taken into account because of the well-known tendency for the disease to be milder and more remittent in children than in adults. A similar analysis of 128 further cases, making a total of 254, gave exactly parallel figures to those in Table XVI.

The most important point brought out by this table is that almost four-fifths of the cases admitted within the first ten days of the fever showed the high continued type of temperature curve. Further, the figures happen to be the same in the case of both adults and children, thus bearing out the conclusion already come to from the long duration of the pyrexia that typhoid is a more severe disease among children in a tropical climate than it is in temperate Europe.

On the other hand, in the much smaller series of cases admitted after the tenth day only 50 per cent of the adults and 33 per cent of the children showed the high continued type of fever. Nevertheless, taking the whole series of 126 cases a little over 70 per cent showed this type, while it was usually apparent within a few days of admission, and for some time past a knowledge of this fact has proved of great value in actual practice in enabling cases of typhoid to be correctly diagnosed in a very early stage, and often at a time when the serum test gave negative results, although later on typical reactions were obtained.

Among the charts not showing the high continued type the most frequent variation was a remittent curve in which the diurnal variation extended over more than 2° F. They include, firstly, cases in which the pyrexia reached 104 or 105, but showed a greater ampli-

CHART 16 (Case 13)



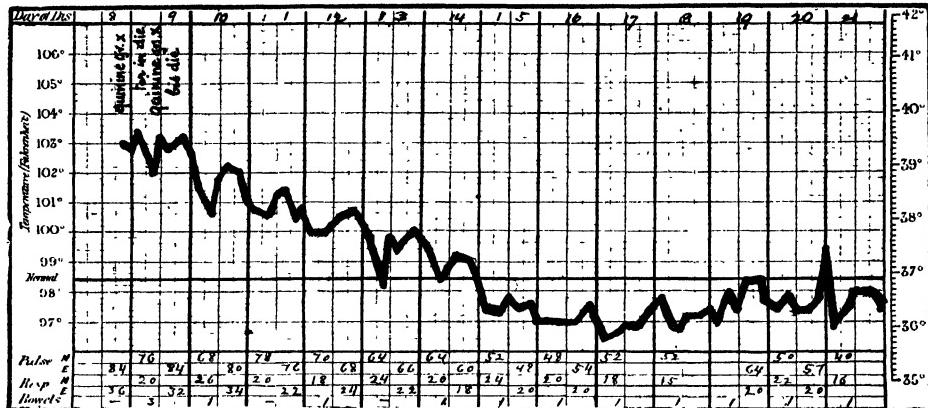
Severe typhoid with high remittent pyrexia terminating fatally on the thirteenth day.
Typhoid bacilli cultivated from finger blood on tenth day.

tude than in the continued type as defined above, and fall within Curschmann's "continuo-remittents." They were all typical severe typhoids, two of them terminating fatally, one of which is illustrated in Chart 16, the typhoid bacillus having been cultivated from

FEVERS IN THE TROPICS

his finger blood taken in a sterile citrate tube. Secondly, there are the mild remittent and abortive cases with a temperature declining below 101°, as in Chart 17 below.

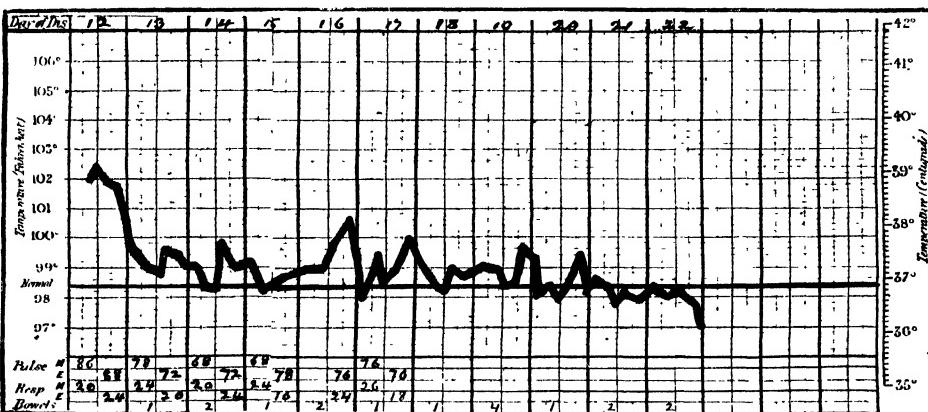
CHART 17 (Case 983)



Mild typhoid with low remittent fever and slow pulse ending on the fifteenth day.
Widal positive 1 in 100 on the ninth day.

One case only showed a "low continued type," by which I mean a temperature curve with a diurnal amplitude not exceeding 2° F., but falling below 101° F. The importance

CHART 18 (Case 984)



Very mild typhoid with intermittent fever after the twelfth day, typical spots and a positive Widal to 1 in 40 on the twenty-fifth day.

of this distinction, which is an artificial one, is that this type is very rare in typhoid, but

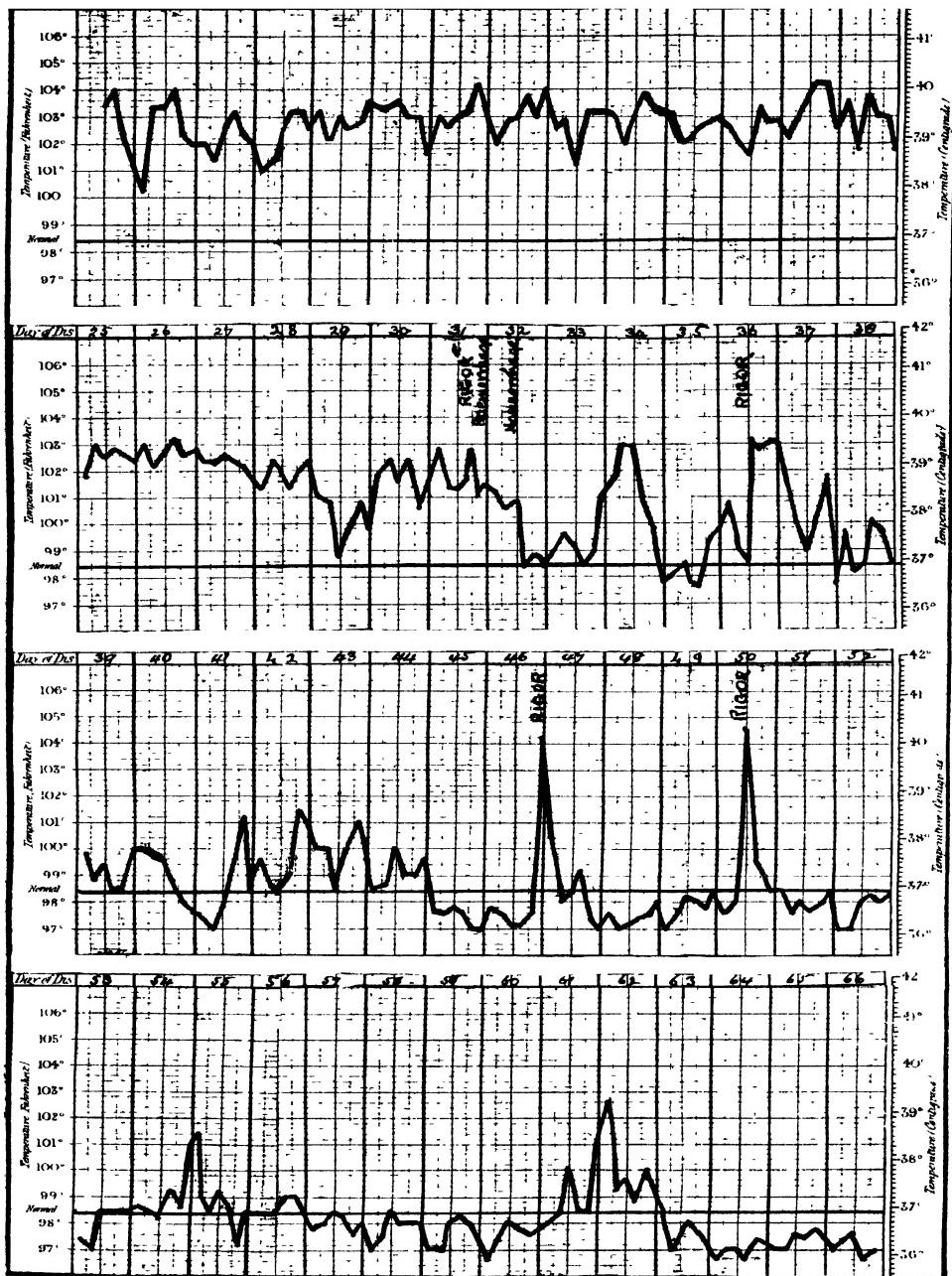
comparatively common in the earlier stages of kala-azar, which has been so often erroneously diagnosed as typhoid. It is illustrated by Chart 5 on p. 28 in an early stage of kala-azar.

Lastly, but again very rarely, although it is somewhat more common in children than adults, a mild typhoid may show an intermittent curve nearly throughout the disease. Chart 18 illustrates this unusual form of the disease, which may easily be overlooked if a Widal's test be not done.

Stage of Steep Curves or Decline of the Temperature.—This is the most variable stage in European typhoid both as to its duration and type, while it has little diagnostic importance. The main point to be noted is that in tropical typhoid this stage tends to be often unduly prolonged and to pass into an intermittent form lasting for days, as in Chart 24, p. 134. The very marked daily variations of 5° or more described by Curschmann in this stage I have occasionally seen as in a native woman, in whom no cause for it could be found, but who ultimately made a good recovery. The sudden decline of the temperature by crisis is occasionally observed in Europe, but I have only met with this once in a native on the eleventh day, the blood giving a serum reaction up to 1 in 100 dilution, thus these puzzling variations would fortunately seem to be very rare.

Stage of Convalescence.—After the decline of the temperature to normal Curschmann describes a stage of sub-normal readings between 96·8° and 97·6°, with but slight daily fluctuations, lasting for one and a half to two weeks, and followed by a rise again to the normal line. This stage is quite exceptional, in my experience, in the tropics, and when it does occur its duration is quite short, usually only two or three days. As a rule, once the temperature has finally reached the normal, often after slight intermittent rises for several days, it keeps close to the normal line. Moreover, typhoid very rarely shows the prolonged low intermittent rises to 99° or 100° F. or more, which are so characteristic of kala-azar in the interval between the higher remittent paroxysms, as shown in Chart 2, facing p. 28, a point of great diagnostic value between early kala-azar and typhoid.

Another exceptional feature of the convalescent stages of typhoid in the tropics is the occurrence of occasional high paroxysms preceded by rigors, and recurring every few days at irregular intervals. Sometimes these may be due to malaria complicating the disease, as in a case in which malignant tertian parasites were found accompanied by a large mononuclear increase, during the high continued fever of typhoid, and sixteen days after the temperature fell to normal a malarial paroxysm, rapidly yielding to quinine, appeared. In other cases, however, rigors and high paroxysmal fever during convalescence from severe typhoid may occur independently of malaria, and sometimes without any cause being found. Chart 19 illustrates such a case, in which no malarial parasites could be found, even in a slide taken when no quinine had been given for several days, while there was some increase of the total leucocytes without any large mononuclear excess. Quinine, even hypodermically, had no effect, but ultimately the patient made a good recovery, although much anxiety was occasioned by this uncommon complication, the precise cause of which was never ascertained. It may possibly have been due to an undetected cholecystitis.



Severe typhoid with prolonged high continued fever, followed by intermittent paroxysms with rigor of uncertain origin.

Recrudescences and Relapses.—In 5 cases out of 126 in the first series and 2 out of 135 in the second series, making 2·7 per cent of the total series, after the temperature had declined by lysis almost to normal a recrudescence of the fever occurred. The temperature rose gradually once more to a considerable height, showing the high continued type in 3 and a remittent one in the other 2 of the first series. In one case the recrudescence was due to eating a cake supplied by a parent, but in the other 4 it was spontaneous, and the fever ran a prolonged course, its total duration being from thirty-two to fifty-eight days, but all of them eventually recovered.

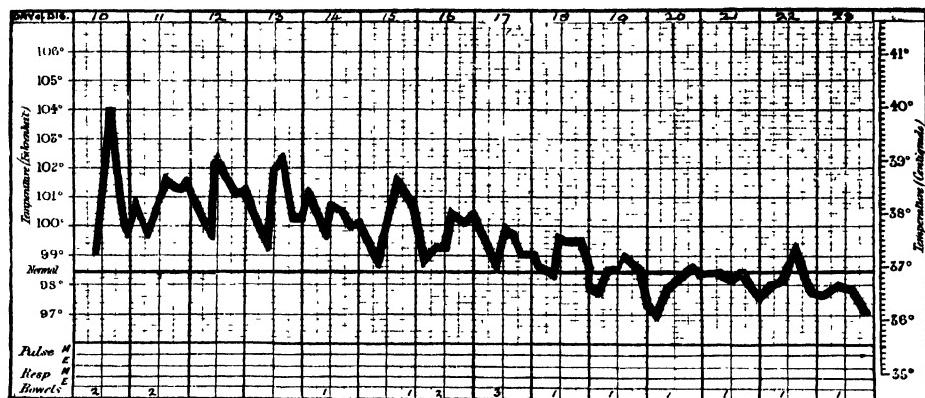
In 6 more cases of the first series and in 11 of the second, making 6·2 per cent of the total cases, actual relapses took place after the temperature had been normal for from one or two up to seven days, although in none of them had it reached a sub-normal point during the apyrexial interval, but had usually risen to 99° in the evening, a feature which is in accordance with Curschmann's experience in Europe. In the first series the total duration from the commencement of the primary rise to the final cessation of the fever varied from thirty-six to forty-two days in 1 of the cases, and was fifty-one to sixty-seven days respectively in the other 2, but all of them eventually made a good recovery, as is usually the case in Europe. One patient was also admitted during a relapse of a mild nature. The proportion of recrudescences and relapses in my two series was 8·9 per cent against 13·8 in Curschmann's much larger series, so that the long average duration of tropical typhoid is not due to excess of relapsing forms of the disease.

Mild Remittent and Abortive Cases. The last point regarding the temperature curve which has to be considered is the very important one, from the diagnostic standpoint, of the frequency of mild remittent and abortive cases which are so liable to be overlooked in a tropical climate.

Mild remittent cases of typhoid include those in which the diurnal variations of the temperature extend over more than 2° F., but in which the temperature does not remain above 101° for two or more days; these cases differ from the high remittent type usually seen in severe cases in this respect. It is just this class of low remittent and intermittent typhoids which is so difficult to recognize in the tropics, as the cases may run a very mild course with few if any characteristic symptoms. Such cases formed 16 per cent of the total, in addition to which there was one of low continued fever, and two other abortive ones, making 17·8 per cent in all of atypical cases. Chart 20 illustrates the low remittent type of fever, while one which was intermittent after the first day in hospital is shown in Chart 18, p. 108, Widal reactions in dilutions of 1 in 100 being obtained in each, while well-marked typhoid spots were present in the last. The duration of the fever was on the average shorter in this series than is usual in tropical typhoid, although not very markedly so, for in half of them the fever lasted over three weeks, while in only 3 did it last under nineteen days. Moreover, 13 out of the 20 cases were admitted within the first ten days of the fever, so that in the majority of them the low remittent type seen was not due to their having come under observation in a late stage of the disease, although in the remaining third this may have been the case, for in some a history of continued fever before admission was obtained. The ages were also fairly uniformly distributed, only 4 of them being children up to 15 years.

In proportion to the total number of cases in each class these mild cases were twice as frequent among immigrants as among Indian-born Europeans, in spite of a slight

CHART 20 (Case 860)



Mild typhoid with low remittent fever. Widal positive 1 in 100 on the fourteenth day.

excess of children among the latter, so that typhoid appears, if anything, to be slightly less virulent among immigrants than in Indian-born Europeans.

Abortive cases are those in which the fever does not exceed fifteen days in duration, but they formed only 3·9 per cent of the total number, excluding fatal cases, being thus

CHART 21 (Case 15)



Abortive typhoid not suspected until a brother and sister were admitted for the disease.
Widal 1 in 100 on the fifth day of pyrexia.

decidedly rare. (Chart 13, p. 104, of a case admitted on the first day of the fever is a good example, and the shortest case I have met with. Another very definite case, shown in

Chart 21, is that of a girl aged 15 admitted on the eighth day of a remittent fever, which terminated on the fourteenth day, no suspicion of typhoid having occurred during this time. On obtaining positive Widal reactions with blood of a small brother and sister of hers, who had been admitted into another ward under a different physician, I tested this patient's blood also and found both a positive Widal reaction up to 1 in 200, and 50 per cent of lymphocytes with only 4·8 per cent of large mononuclears. This result was obtained just in time to save her being put on a solid diet very soon after her temperature reached normal. A few days later another brother and sister were admitted for typhoid, all five patients coming from one house. In these mild cases a marked lymphocyte increase without any excess of large mononuclears is often early present, and should lead to a Widal test being performed. Two of these cases showed the low remittent type of fever, but the other 3 showed a high continued typhoid type, only of unusually short duration.

These mild remittent and abortive cases are exceedingly difficult to diagnose in the tropics without a blood examination, and have doubtless very often been returned as "remittent fever," which has long been one of the official synonyms for malaria, and as "simple continued fever," under which doubtful fevers of all kinds are too often entered, whatever the type of temperature may be, although I know of no definite fever to which this term might be suitably applied, unless it be the more continued types of the seven-day fever described on p. 297.

ANALYSIS OF THE SYMPTOMS OF TYPHOID FEVER

History of Onset and Prodromal Symptoms.—Although, as already mentioned, the temperature more frequently rises rapidly with chills or rigor in the tropics than in temperate climates, nevertheless a typical history of preceding lassitude, headache and loss of appetite and gradual onset was noted in over half the cases, and is of considerable diagnostic value, especially in differentiating the early stages of typhoid from seven-day fever, which almost invariably has a sudden commencement. Aching pains in the back and extremities are not infrequently complained of in early typhoid, but are not of as severe and sudden a character as in seven-day fever. Epistaxis was only noted in 3 per cent of this hospital series, while it is not uncommon in the later stages especially of kala-azar. Lassitude may also occur for a day or two only, as a rule, before the onset of malarial fevers. Repeated chilliness may also be noted in cases of typhoid with a gradual onset, so that on the whole the prodromal symptoms of the disease are of less diagnostic value in typhoid in the tropics than in temperate climates.

General Appearance.—The flushed face, apathetic look, low dorsal decubitus and the thickly coated tongue, often with red edges and tip, are present in all but the mildest cases of typhoid. They present a marked contrast to the comparatively slight general symptoms in the early stages of kala-azar during high remittent fever. They may, however, be closely simulated by the more continued type of seven-day fever with flushed face and dull look, and thus lead to typhoid being suspected, although the sudden severe pains and severe frontal headache, together with the saddle-back remission just when

the steady rise of temperature of typhoid is to be expected, will usually enable the seven-day fever to be early recognized.

The Pulse.—After the temperature curve, perhaps the most important aid in the differentiation of typhoid in the tropics is the pulse rate, which is well known to be disproportionately slow as compared with the degree of pyrexia in this disease, a feature which is, however, less marked in women and children than in the case of men. Table XVII. shows the pulse rates in those of my Calcutta typhoids in which it has been

TABLE XVII. PULSE RATES IN 224 CASES OF TYPHOID WITH A TEMPERATURE RISING TO 103° OR OVER

	Pulse not over 100 throughout	Pulse not over 100 for two or more days	Pulse over 100 throughout during high fever
Men	57	41·6	28
Women	1	2·9	29
Children	1	1·9	52
			98·1
	38·0	11·8	20·0

sufficiently frequently recorded, divided in accordance with whether the rate did not exceed 100 per minute for two or more consecutive days, while the temperature reached 103° F., or higher, or whether the pulse was over that rate.

These figures are in agreement with European experience both as regards the frequency of a pulse relatively slow as compared to the temperature, in typhoid, and its less incidence in women and children than in men, although this latter feature is more marked in the women of my series than I had been led to expect from the statements in European literature. That in children a slow pulse is rare during typhoid is well known, but its rarity in adult females is worth bearing in mind, as it makes the pulse rate of much less diagnostic importance in tropical cases of typhoid when dealing with both women and children. The fact that as many as 80 per cent of the male cases showed a pulse not exceeding 100 during pyrexia reaching over 103° F., for two or more days, most frequently in the early difficult stages of the disease, is of great diagnostic importance, because such a relatively slow pulse is rare in those other fevers which are liable to be confused with typhoid, with the single exception of the seven-day fever as described on page 296; and it is to be remembered that the latter disease only exceptionally shows the high continued type of the pyrexia of typhoid. On the other hand, in severe malarial remittent fevers, whose temperature curves alone in any way resemble typhoid, the pulse is almost invariably rapid and usually well over 100 during high pyrexia. In Malta fever, again, Hughes states that in the severe typhoid-like cases the pulse is commonly rapid. In the early stages of kala-azar with high remittent or continued fever, the pulse is usually rapid during high fever even in men, although Chart 8, p. 31, is an exception as in this case the pulse was slow all through, and I have one other chart showing a high continued fever with

a slow pulse at the beginning of kala-azar, in which, however, the blood count enabled me correctly to diagnose the case before any typical symptoms were present.

A combination of a slow pulse with a high continued temperature curve is especially diagnostic of typhoid fever, while these features are most commonly found in the early stages, when the diagnosis is most difficult, and their conjoint occurrence is almost a certain indication of typhoid.

A pulse which persistently rises to over 100 a minute in typhoid in men is of bad prognostic significance, for out of 13 such cases 5 died, in 3 of whom this rapidity of the heart was apparent before the general condition had become grave. Dicrotism of the pulse is also frequent in typhoid in the tropics, but it is not peculiar to this fever, and is often absent in the early stages, so is not of much diagnostic value.

The Heart.—The tendency of the first sound of the heart to become short and faint in typhoid is well known, and the diagnostic import of this symptom in India was pointed out by G. H. Young in 1887, and may be regarded as an indication for cardiac stimulants, especially during very hot weather.

The Lungs.—The frequency and diagnostic importance of the presence of physical signs in the lungs, especially a dry congestive affection of the smaller bronchi, is fully recognized by writers on typhoid in temperate climates. Table XVIII. shows the affections of the lungs met with in the Calcutta series.

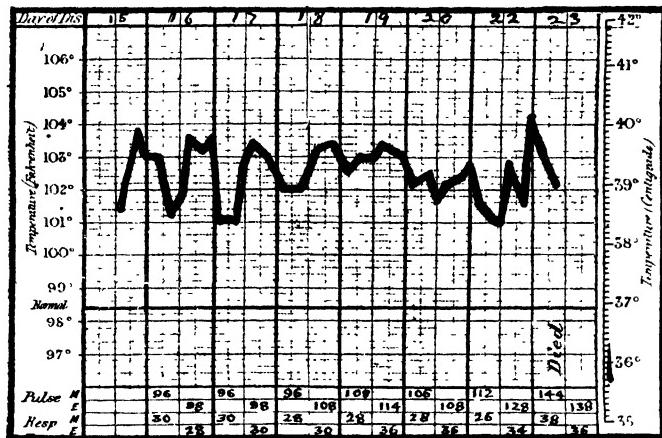
TABLE XVIII.—LUNG COMPLICATIONS IN TYPHOID IN THE TROPICS

Normal on admission	72	58.1 per cent
Bronchial râles, etc., present	10	32.2 "
Pneumonic consolidation	12	9.7 "
Total lung complications	52	41.9 per cent

Thus, nearly half the cases showed some lung complication, although in many of them the condition of this organ had only been noted on admission, so that there can be no doubt that if the physical signs at different periods of the fever are regularly recorded the proportion showing bronchial congestion would be still larger as in Europe. The pneumonia was chiefly of the hypostatic type, affecting the bases of the lungs in the more severe and frequently fatal cases. Broncho and lobar pneumonia were also met with, the former occasionally occurring early in such a manner as to overshadow for a time the typhoid symptoms, but the prolonged course of the pyrexia, extending much beyond seven days, led to a suspicion which was confirmed by positive Widal tests for typhoid. In one case pleurisy was present in addition, and in another fatal general miliary tuberculosis supervened on an attack of typhoid in a patient in whom tubercle was suspected on admission. Another case of great interest had been sent into hospital for liver abscess, as he showed some enlargement of that organ together with signs of pleurisy at the right base. Leucocytosis was found to be absent, while a positive Widal up to a 1 in 100 dilution was obtained and typhoid diagnosed. An exploring needle revealed only pleuritic fluid,

and on the patient's death the diagnosis of typhoid and the absence of liver abscess was confirmed post mortem (see Chart 22).

CHART 22 (Case 877)



Patient admitted for liver abscess. Blood examination showed only 5250 leucocytes and positive Widal reaction to 1 in 100. The presence of typhoid with right basal pleurisy, but healthy liver, verified post mortem.

The presence of physical signs of bronchial congestion with little or no sputum is considered by Curschmann to be very constant in typhoid, and of a specific nature. Its frequency in this disease in the tropics is, therefore, of great importance, because most other tropical fevers which resemble typhoid rarely show this complication. Thus, lung signs were only found in 4 per cent of my seven-day fever cases, while I find it is also very unusual in the earlier typhoid-like stages of kala-azar, although the terminal ones are frequently complicated by pneumonia and occasionally by phthisis. On the other hand, both bronchitis and hypostatic congestion of the lungs are common in severe or prolonged Malta fever according to Hughes.

The Digestive System.—The tongue and mouth are often dry in an early stage of typhoid, but the conditions met with are variable. In about one-third of the Calcutta cases furring in the centre with red tip and edges was noted, while in another third fairly uniform coating was observed. In the remaining cases the very foul and often cracked tongue of severe typhoid was present. On the whole the changes are not of much diagnostic value, for the red-edged variety is very common in seven-day fever, while the uniform furring is nearly constant in malaria, and not uncommon in kala-azar. The early stages of the latter disease, however, may not infrequently display a nearly clean tongue with persistent high fever, and very rarely, if ever, show the dry cracked organ of severe typhoid.

Sickness.—As in European experience vomiting was not very common in my typhoid cases, having only been noted in one-fourth of all cases, in several of these only after

taking medicine. The only case in which sickness was very marked was one of perforation of the small intestine. It is also rare in early kala-azar, but very common in malaria, and fairly so in seven-day fever.

The Bowels.—Table XIX. shows the state of the bowels in the Calcutta typhoid cases subdivided into (1) those with diarrhoea throughout; (2) those with transient diarrhoea,

TABLE XIX.—THE BOWELS IN 257 CASES OF TYPHOID IN THE TROPICS

	Calcutta Series.					Curschmann's 13 Years' Leipsic Cases.		
	Total Cases.	Per- centage.	Children.	Per- centage.	Fatal Cases.	Per- centage.	Cases	Per- centage.
Diarrhoea throughout .	59	22.9	9	15.3	23	62.2	480	29.5
Transient diarrhoea .	96	37.4	22	37.3	8	21.5	694	42.7
Normal or constipated .	102	39.7	28	47.4	6	16.3	452	27.7
Total	257	..	59	..	37			

and (3) those with normal or constipated stools throughout; Curschmann's figures being also given for comparison.

Here once more the data derived from my small series of cases agree very fairly with those of Curschmann's extensive statistics of typhoid in Germany, and illustrate once more the fact that typhoid in the tropics differs in no essential feature from the disease in temperate climates. In only one-fourth of the total cases was persistent diarrhoea present, the stools then being commonly of the typical pea-soupy character, yet no less than two-thirds of the deaths occurred among this class of cases, showing that diarrhoea throughout the disease is of specially bad prognostic import. The remaining three-fourths of the cases are equally divided between the class with occasional or transient diarrhoea, and those with normal or constipated motions throughout, constipation being far more frequent than normal stools. There was but little difference in the death-rate of these two last classes. The cases occurring in children up to 15 years of age are also shown in a separate column, from which it appears that persistent diarrhoea is specially rare among them, while over half showed constipation throughout. This is in accordance with the comparative mildness and low death-rate of typhoid in children.

The Abdomen.—One of the most important features of typhoid in the tropics, as elsewhere, is the state of the abdomen, which it is essential to watch closely day by day. The following were the conditions noted in the first Calcutta series. Distension of the abdomen was recorded in no less than 77 per cent, and in 80.3 per cent of a second series of 127 cases, while in 32 per cent it was of a specially marked degree. In 8 per cent there was pain in the abdomen, and in 7 per cent more either tenderness or gurgling was noted in the right iliac fossa, leaving only 8 per cent in which no abdominal symptoms had

been described in the clinical records, and in nearly all these only the condition on admission had been recorded, but it may have been present to some extent later in some of them. Thus, we find that some abdominal signs are nearly invariably present in the course of typhoid fever, while they are commonly a very prominent feature of the affection. Gurgling in the right iliac fossa was seldom noted in this series because it was rarely sought for, this symptom being so often detected in other conditions that it has little or no diagnostic value in typhoid; indeed it has always appeared to me to be most dangerous to attempt to elicit it, when we know that nothing but the thickness of the peritoneal coat at the base of an ulcer may be saving the patient from a fatal perforation.

The great diagnostic importance of even slight abdominal distension in typhoid in the tropics depends on the rarity of this symptom in other fevers which may closely resemble it. Thus, I have met with slight abdominal distension in only 3 cases of kala-azar seen within the first two months of the fever, at which time alone it at all closely resembles typhoid, and in these it was very slight. It is also an uncommon symptom, apart from dysenteric complication, in the later stages. In Malta fever Hughes states that tympanites is a rare symptom and seldom marked, although epigastric tenderness is not uncommon. In relapsing fever epigastric tenderness, but not general distension, is frequent. In seven-day fever, however, some degree of abdominal distension occurred in nearly one-fifth of my cases, and the abdomen was the seat of pain in as many more; this pain is rarely very marked or persistent.

The Liver is only occasionally slightly enlarged in typhoid in temperate climates, but in nearly one-fourth of my Calcutta series some degree of increase in the size of this organ was detected. It was nearly always slight in degree and the organ is but seldom tender, while no serious affection of the liver was met with.

The Spleen.—Great stress is rightly laid on the diagnostic importance of enlargement of the spleen in typhoid in temperate climates. Curschmann found this physical sign in from 75 to 80 per cent of his cases by percussion, while in his large Hamburg series the organ was palpable below the costal margin in 34 per cent, some degree of enlargement being not uncommonly detected by the end of the first week of the fever. In the tropics enlargement of the spleen is so frequently produced by malaria, kala-azar, Malta and relapsing fevers that this symptom loses much of the diagnostic value pertaining to it in Europe.

In 209 Calcutta cases, as a rule, only such degrees of enlargement as allowed of the organ being palpated below the ribs were recorded, and in 30·1 per cent of the cases the spleen reached this size; this is in agreement once more with Curschmann's figure for a similar condition. In 5 cases the organ extended 2 or 3 in. below the costal margin, but in no case was the extreme enlargement to the navel or beyond, which is so frequent, even in fairly early cases of kala-azar, met with: an important point of distinction between the two diseases. In seven-day fever the spleen was only palpable in from 2 to 7 per cent; against 22·3 per cent of typhoid cases on admission in the first week of the disease, so that enlargement of the organ is in favour of typhoid as against seven-day fever. With these exceptions the size of the spleen in typhoid is of little diagnostic value in the tropics.

The Urine.—In temperate climates typhoid usually shows a high-coloured urine with a specific gravity of over 1020, while albumen was found by Curschmann in from 15 to 20 per cent, and by Osler in 74 per cent, including traces detected by delicate methods. In the Calcutta series the data on this point are incomplete, the urine having in many cases only been examined on admission. Albumen was found in about one-sixth of the cases, but the only one in which it was extensive was complicated by Bright's disease.

The Diazo Reaction has also been too much neglected in the tropics, for although it certainly occurs in many other conditions besides typhoid fever, yet it is so nearly constant in the latter disease that a negative result goes far towards excluding that affection. In 1894 Tull-Walsh carried out this test in a number of typhoid and "remittent" fevers in Calcutta and came to the conclusion that it was of little diagnostic value, but a further series of cases with control Widal and blood tests with our present knowledge would very possibly yield more valuable results. The diazo reaction is certainly frequently absent in early cases of kala-azar, as well as in malarial fevers, but data are not at hand to show the frequency with which it may occur in tropical fevers other than typhoid. Bassett-Smith advises this test to be performed in the following way.

Solution A. 50 c.c. hydrochloric acid diluted to 1000 c.c., and then saturated with sulphanilic acid. Solution B. 0·5 per cent solution of sodium nitrite. Immediately before use mix 1 part of B with 40 parts of A. Add to the urine an equal quantity of the mixture of A and B, and then shake to form froth. Run a little strong ammonia down the side of the tube to form a colourless layer on the top.

A carmine ring above the urine, with pink froth, constitutes a positive reaction; an orange ring, with yellowish froth, an indefinite one; and a yellow ring with no change in the colour of the froth, a negative one. If in doubt, pour the whole on to a white dish with some water in it. A salmon-red colour means a positive, and an orange only a negative reaction.

COMPLICATIONS OF TYPHOID IN THE TROPICS

Haemorrhage from the Bowels.—The most frequent and grave complication met with in the Calcutta series was undoubtedly haemorrhage from the intestines. In both Curschmann's Leipsic and Osler's Baltimore cases it was met with in 6 per cent of the total, although the former writer states that in individual outbreaks he has met with it in as large a proportion as 10 to 14 per cent. In the two Calcutta series haemorrhage occurred in 34, or 14·8 per cent of 230 cases, excluding two in which only a trace of blood was detected, as such cases are not included in Curschmann's figures. This great frequency of haemorrhage in the tropics may in part be due to the greater severity of the disease, as evidenced by the longer average duration of the fever curve which has been already pointed out. Another possible factor is a greater variation in the coagulability of the blood in typhoid in a hot climate, for the opposite variation of increased coagulability leading to thrombosis was also unusually frequent in Calcutta.

As, according to Wright, both these complications are preventable and haemorrhages are specially fatal, the occurrence of this complication deserves close study. As the loss

of blood varies greatly in amount, I have divided my first series of cases into two classes in accordance with whether the haemorrhage was sufficient to depress materially the temperature or quicken the pulse, or whether blood was only detected by examination of the stools and no serious constitutional disturbance was caused. The former more severe degree occurred in 13 cases, 7 of which terminated fatally, just one-third of the total deaths being due to haemorrhages from the bowel. In 9 more the less serious degree of malaena occurred, none proving fatal, so that the mortality of both classes combined was 7 out of 22 cases, or 32 per cent, which differs but slightly from Curschmann's estimate of the deaths at 20 to 30 per cent. He also points out the rarity of this complication in children; all my cases occurred in persons of over 15, except two in children of 11 and 13 years of age respectively, in one of whom it proved fatal.

If serious haemorrhages in typhoid are due to a preventable reduced coagulability of the blood, as maintained by Wright—and the occurrence of purpuric haemorrhages at the same time as that from the bowel in two of my cases would support his contention—then it becomes a matter of great importance to ascertain if this complication is associated specially with any particular class of case. A careful examination of my notes shows that such is the case, for on working out the frequency of diarrhoea among the haemorragic cases no less than 32 out of 36, or 88.9 per cent, had shown looseness of the bowels at some stage of the disease, while 19, including 13 out of the 18 severe cases, had suffered from diarrhoea throughout the disease, and only 4 showed constipation throughout, in 3 of which the haemorrhage was slight. When we remember that only 22.9 per cent of the total cases showed persistent diarrhoea, while 39.7 per cent showed constipation throughout, then it becomes clear that there is a definite association between intestinal haemorrhage and looseness of the bowels in typhoid in the tropics, both being dependent on severe local lesions in the ileum. The importance of the recognition of this relationship is obvious, for it is specially in cases with marked diarrhoea that the coagulability of the blood should be most closely watched for delayed action, and appropriate steps taken to prevent the impending calamity by the means referred to on page 135.

In this connexion the stage of the disease at which haemorrhages are most frequent is of importance. Curschmann met with this complication within the first two weeks in 30 per cent, when it may be copious, although it must come from the swollen Peyer's patches, as sloughing will not by that time have taken place. In the remaining 70 per cent the haemorrhages occurred in the third week or later. In only 3 of the 22 Calcutta cases did malaena occur during the first two weeks, and in 2 of these it was slight. In the third week this symptom was met with in 10 cases, 8 of which were severe; in the fourth week there were 4 cases, 2 being severe; and at a still later date 2 cases on the thirty-third and forty-sixth day respectively, the latter being fatal. In the remaining 2 the date was doubtful, 1 fatal one being admitted late in the course of the disease without any clear history being obtainable. In all but 2 of the severe cases, then, the haemorrhage occurred during the third or fourth week, when the sloughs would be separating, so that the coagulability of the blood should be especially examined at that period for delayed clotting, as this predisposes to serious haemorrhages.

Thrombosis.—The opposite condition of increased coagulability of the blood pre-

disposing to thrombosis is a much rarer complication of typhoid in temperate climates than is haemorrhage. Murchison stated that it occurred in but 1 per cent of typhoid fevers, while Curschmann and Osler in Nothnagel's *Encyclopædia* do not give the exact proportion in which they met with it. This complication appears to be much commoner in the tropics than Murchison's figure, for in 260 Calcutta cases thrombosis occurred in 9, or 3·5 per cent. Sir Joseph Fayrer called attention to the frequency of pulmonary thrombosis after severe operations in the tropics, and the same tendency may show itself in the greater frequency of thrombosis during typhoid. Of the 7 cases in my first series 1 occurred in a man of 46, and 6 in men of from 21 to 30 years of age. In 5 the femoral vein was involved, and in the remaining 2 the tibials. The earliest date of onset was the nineteenth day; in 3 in the fourth week, in 2 on the thirtieth day, and in the remaining 1 on the forty-fourth day of the disease, the last patient having also previously suffered from slight haemorrhage on the twenty-third and twenty-fourth days, thus indicating marked variations in the clotting power of his blood in the course of the attack of typhoid. The complication occurred about equally in mild and severe cases. Chart 23 is that of a very mild type being followed by thrombosis. Only 1 of these patients belonged to the constipated class of typhoids, all the others having suffered from diarrhoea, while in 3 of them it had been persistent throughout; so that thrombosis, as well as malaena, is especially associated with looseness of the bowels, thus emphasizing the special need to watch the coagulability of the blood in all cases of typhoid with marked intestinal symptoms.

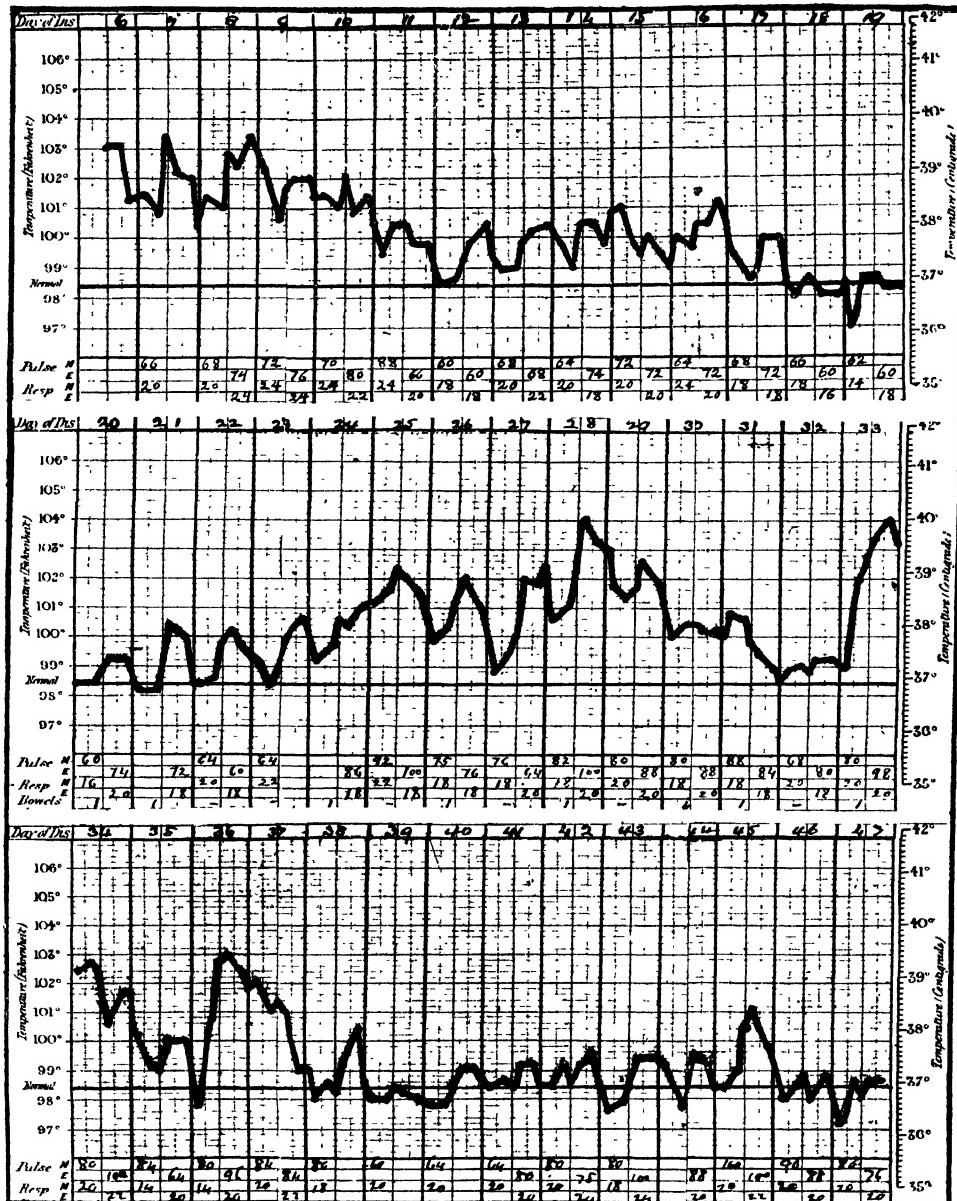
Periostitis.—This rare complication occurred twice, once at the usual site over the tibia, resulting in an abscess, while, in the other, great pain and tenderness in the left arm appeared, not in relationship to the blood-vessels, and accompanied by leucocytosis (23,000); it subsided without suppuration, and was looked on as periostitis of the humerus. I have also seen suppurative periostitis of the tibia in a native patient after typhoid fever.

Perforation of the Intestine.—This terrible complication occurred three times in 259 cases, or in 1·16 per cent. The first case occurred on the twentieth day of a very mild attack with intermittent fever during the third week of the disease. The patient was thought to be suffering from appendicitis, and this organ was removed and contained two small ulcers. He died on the following day and extensive typhoid ulceration with perforation was found. In the second case it happened on the twenty-fourth day of a severe case, and the patient died an hour and a half after the sudden onset of serious symptoms.

Other Complications.—In one case abortion took place on the twentieth day, but although the pyrexia was prolonged to the twenty-seventh day, the patient made a good recovery. Parotid abscess of a very acute and fatal nature was once seen in the fourth week, and acute mastitis in another. Fatal mania followed a prolonged mild case in a woman aged 22, and hyperpyrexia to 106·6 terminated the life of a man aged 34.

Mortality.—There were 40 deaths among 276 cases in my Calcutta European series; a mortality of 14·5 per cent. This figure is higher than Osler's for ten years in Baltimore with 7·5 per cent and Curschmann's thirteen years' experience in Leipsic with 12·7 per cent,

CHART 23 (Case 537)



1 typhoid with low remittent temperature touching normal on the twelfth day, but complicated by femoral thrombosis on the twenty-second day.

or including his private cases, which were probably seen much earlier than hospital ones, of 9.3 per cent. The mortality in the British Army in India used to be much higher, but in the same years as my Calcutta series, namely, from 1904 to 1908, it varied from 15.5 to 18.1 per cent, with a mean of 16.8, figures which are also strictly comparable with the Calcutta ones because they relate to a period shortly before inoculation was extensively used in the Army and paratyphoids were separated from true typhoids. The lower mortality in Calcutta is accounted for by a number of children in my series, among whom the mortality was only 6.9 per cent. In Hongkong Clarke records a mortality in Europeans over a period of fifteen years of 22.8 per cent, while in Chinese it was as high as 78.5 per cent, only very bad cases being brought to hospital, and in other Asiatics 23.4 per cent. In a series of Indian patients treated in the Calcutta Medical College Hospital, and verified by Widal reactions, I found the mortality to be 26 per cent, many of them being admitted late in the disease.

In persons **inoculated against typhoid** the case mortality is distinctly less, as shown by the following figures of the British Army in India :

TABLE XX.

Year	Inoculated.			Uninoculated.		
	Cases.	Deaths.	Percentage	Cases.	Deaths.	Percentage
1911	106	11	10.7	64	11	17.2
1912	78	10	12.8	40	16	40.0
1913	61	8	13.1	24	8	33.3

The protective effect is very much lessened after two years, when inoculation should be repeated.

CLINICAL FEATURES OF TYPHOID IN NATIVES OF INDIA

In 1902 I analysed the symptoms of 11 cases of typhoid in natives of India in the Medical College Hospital, Calcutta, and found no essential differences from the same disease in Europeans, although the mortality of 30 per cent was higher, apparently on account of the late stage at which many of them were brought to hospital. I now have records of 50 such cases (not including those among immigrant Chinese and Armenians) with a mortality of 26 per cent, but the whole clinical picture is so precisely similar to that derived from the above consideration of typhoid in Europeans in India, that it is unnecessary to describe the native series in detail. The following points will suffice to illustrate the identity of the two series, and to bring out such small variations as exist between them.

The disease occurred among all classes, Hindus, Mohammedans and native Christians, the largest numbers in proportion to the population being in the latter class, owing to the fact that they bring their children more readily to the hospital. Out of 20 Indian

Christians 75 per cent were not over 15 years of age and only 25 per cent over that age, although other classes of native children are rarely admitted. One patient was a Parsee ; these people are not infrequently attacked by typhoid in Bombay. In proportion to the relative numbers in Calcutta, Hindus suffered more than Mohammedans. Including a further series out of 70 cases in Indians the age was over 25 years in only 29 per cent and below 25 in 71 per cent.

The duration of the fever showed only 9 per cent of over thirty-three days' duration and 56 per cent between twenty-two and thirty-three days, the average duration being shorter than those in the European series, and more closely corresponding to that met with in temperate climates. Only one non-fatal case of under fifteen days' duration was met with. This is of interest, as pointing to the long duration of typhoid in Europeans in the hot plains of India being due to their being attacked while in a trying climate to which they are not adapted.

The Temperature Curve corresponds exactly with that in Europeans, the high continued type being even a more constant feature, for it was observed in no less than 89 per cent of cases admitted in the first two weeks of the fever, and in 74 per cent of the total number. In none was the low continued or intermittent form seen. These figures suggest the possibility that some of the milder remittent cases in natives were overlooked and their blood not sent to the laboratory for a serum test.

The general symptoms present few features of special interest. The pulse was less frequently slow than in Europeans, while diarrhoea was more commonly marked, although one-third showed constipation. The stools rarely show a typical pea-soupy character, apparently owing to differences of diet. **Abdominal** symptoms were just as prominent as in the Europeans, either distension, tenderness or gurgling in the right iliac fossa being recorded in 87 per cent. **Spots** were not noted, the dark skins of the hospital class of natives rendering them very difficult to detect. E. Goodeve frequently found them, while G. F. A. Harris, I.M.S., Physician to the Medical College Hospital, informs me that in the fairer upper classes seen in consulting practice he has often been able to detect typhoid spots with a purplish appearance. The spleen was felt below the costal margin in 36 per cent, but never extended more than 2 in. below the ribs. **Congestion** of the bases of the **lungs** or bronchial râles was recorded in 75 per cent, including pneumonia in 10 per cent, affections of these organs having been more frequently recorded in the Indian than in the European series.

Complications were less common in the Indian than in the European series. Perforation of the bowel occurred twice, but fatal collapse took place too quickly to allow of operative procedures being undertaken. Periostitis of the tibia supervened once and haemorrhage from the bowel twice, but no case of thrombosis occurred : the greater rarity of these vascular complications in natives thus bears out the suggestion already made, that their frequency in Europeans in the tropics may be due to greater variations in the coagulability of their blood in hot places.

Widal reactions were obtained in every case ; only fevers giving them have been included in the series. In 84 per cent a complete reaction up to 1 in 100 was obtained,

including some cases re-tested after giving negative or lower reactions at an earlier date. In only one-fourth was a reaction obtained during the first two weeks, many having only been admitted at a later period. A few paratyphoid-like cases, with negative serum reactions to the typhoid bacillus, were also met with, but I have not yet cultivated any organism from them, as they usually only come under my observation at a late date when the peripheral blood is commonly sterile.

The above data will suffice to prove that typhoid in natives of India presents no material points of difference from the disease in Europeans in the tropics, and now that the frequency of the disease among them is so conclusively proved, it should be recognized without hesitation by the same signs already discussed in connexion with the clinical description of the European series.

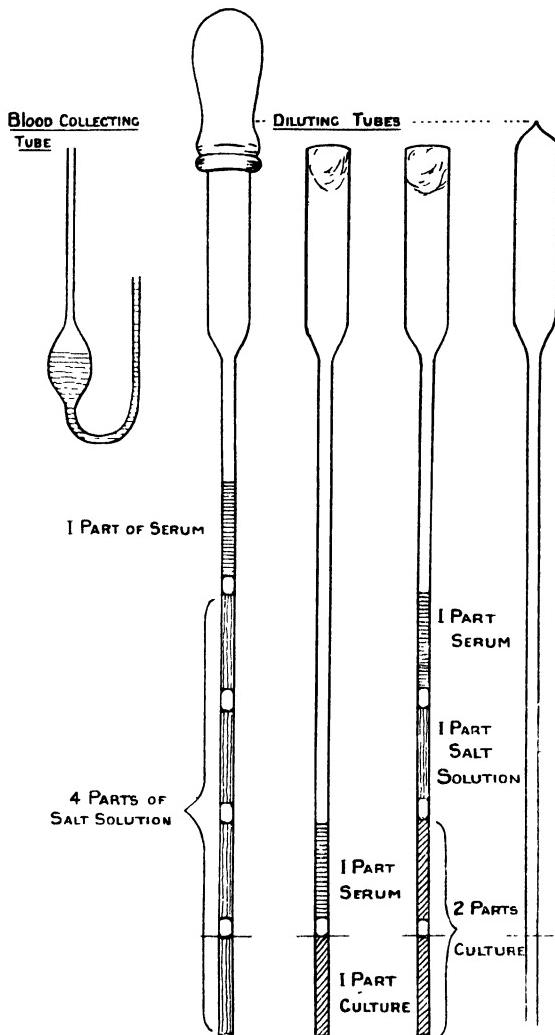
In their **clinical characters** the paratyphoids show no essential differences from typhoid fever itself except that they are on the average both milder and of shorter duration, although severe and fatal cases are not rare. The mortality in the Indian cases shown in the above table is 2·25 per cent, which is probably a fair estimate. Frontal headache and pains in the back and often high fever occur, although the course of the temperature is usually less continued and more of the remittent or even intermittent type than in cases due to the *B. typhosus*, but mild cases of the latter infection are quite indistinguishable from paratyphoids clinically, as are the varieties of the latter from one another, so only cultivation of the different bacilli from the blood, faeces, or urine will enable the diagnosis to be established. As the treatment is the same for all three forms of the disease, this is of little importance as regards the welfare of the patient himself. The usual complications of typhoid may be met with, death sometimes being due to haemorrhage from the bowel, while ulceration of the intestine may be found post mortem, and is said to involve the upper part of the large intestine more frequently than in true typhoid. Relapses after an apyretic interval have also been repeatedly recorded. The bowels more frequently show constipation than in true typhoid in accordance with the milder course of the disease. Intra-uterine infection has been met with. In the Dardanelles a number of cases showed jaundice, probably due to concurrent infection with the epidemic jaundice which was also prevalent at the time. Cholecystitis occurs in paratyphoids due to infection of the gall-bladder, and such cases are especially likely to become carriers. The duration of the fever is said to vary most commonly between 15 and 22 days. Whitham in a review of paratyphoid as seen in the United States Army gives the following figures of the frequency of the principal symptoms :

	Per cent.		Per cent.
Headache	85	Mild intermittent shivering . .	25
Diarrhoea	55	Extreme general weakness . .	25
General abdominal pain	35	Backache	25
Aching in the limbs	30	Epistaxis	20

The close resemblance to ordinary typhoid is here clearly seen. Several cases are on record in which pain in the right iliac fossa has been so severe as to lead to operations being undertaken for appendicitis, when involvement of that portion of the bowel in the enteric inflammatory swelling was found.

THE BLOOD CHANGES IN TYPHOID

Widal's Serum Test.—The most important change in the blood in typhoid is the increase in the agglutinative action on Eberth's bacillus, the estimation of which for



Method of diluting serum for Widal's test by means of Wright's tubes.

diagnostic purposes is known as Widal's test. The methods of carrying it out are as

Microscopical Method.—In doing a Widal test in a laboratory a fourteen- to twenty-hour culture in broth is used for the typhoid reaction, and a four- or five-day agar one for *Malta fever*. The dilutions are most conveniently carried out in the capillary tubes made by melting and drawing out a piece of glass tubing as advised by Sir A. E. Wright, for these can also be utilized for his macroscopical method. In the case of typhoid I always make three dilutions of 1 in 20, 1 in 40 and 1 in 100 respectively as follows. Some of the broth culture being placed in one watch glass, and a little sterile salt solution in a second, a capillary tube is marked with a wax pencil at a small distance from the fine end. The upper end of these tubes may be open and covered by a rubber teat, by means of pressure on which with the thumb and forefinger the dilutions are made, or it may be a closed bulb, which is heated for a second in the flame of a bunsen burner or spirit lamp to expel some of the air, so that while it is cooling and contracting again any fluid beneath whose surface the open capillary end is dipped will run up the tube as long as the contact with the fluid is maintained, and can be expelled again by a momentary reapplication of heat to the bulb. Personally I prefer the latter method, as the manipulations require less delicacy of touch than the use of the rubber teat involves.

To prepare the 1 in 20 dilution, the capillary tube is filled with the serum to be tested up to the mark by dipping its open end into the fluid after heating the bulb. The end is then removed from the serum, and a small bubble of air allowed to enter. Next dip the end into the normal salt solution until a portion of this fluid has run in up to the mark, remove the tube and admit a bubble of air once more, and go on repeating this process until nine measured parts of the salt solution have entered the tube. Now warm the bulb so as to expel the whole of the contents of the tube into a clean watch glass, and a 1 in 10 dilution of the serum will have been obtained. One part of this has only to be diluted in a similar manner with one of the broth culture of typhoid to make a 1 in 20 dilution, which is expelled on to a slide and a cover-glass placed over it. To make a 1 in 40 dilution take 1 part of the 1 in 10 dilution of serum, add 1 of salt solution and 2 of the typhoid culture, so as to have an equal quantity of the diluted serum and of the culture, and place this under a second cover-glass on the same slide, marking each dilution with a wax pencil. To make the 1 in 100 dilution first take 1 part of the 1 in 10 and add 4 of salt solution, then add to 1 part of the resulting 1 in 50 dilution 1 of the typhoid culture and mount as before. The thin cover-glasses should be ringed with a little vaseline to prevent evaporation of the fluid and consequent drying.

On examining a specimen with an $\frac{1}{8}$ -in. lens immediately after putting it up the typhoid bacilli will be found to be actively moving across the field in all directions, but if the serum be from a typhoid patient they will soon begin to run together into clumps, most markedly in the 1 in 20 dilution to start with. The slide should be examined occasionally up to the end of one hour, which is the time limit for the reaction with a living culture, and the degree of clumping noted at the end of this period, if complete reaction has not taken place in the highest dilution before that time has elapsed. The reaction is complete in any given dilution when not only have large clumps formed, but also any organisms remaining free have ceased to move actively right across the field of the microscope. This active movement must be carefully distinguished from the Brownian motion common to all small particles suspended in a fluid, which produces constant circular motion of

the free organisms, but will not rapidly translate them across the field, as when in active movement. This Brownian movement will be found after complete clumping is present. If such complete clumping in the 1 in 100 dilution occurs in well under the hour, it will be found also to take place with considerably higher dilutions, although there is no necessity to go further than a 1 in 100, as reactions in this dilution are reliable evidence of the presence of typhoid.

For Malta fever dilutions of 1 in 40, 1 in 80, 1 in 160 and higher if desired, are made in a similar manner, equal parts of the diluted serum and an emulsion of the culture in sterile normal salt solution being put up.

The Macroscopical Method.—Although I much prefer the microscopical test when facilities for carrying it out are available, yet with due care results of great practical value can be obtained with the macroscopical method : this has the advantage that an emulsion of dead typhoid bacilli or the microcoecus melitensis and some glass tubing are the only requisites for the test, so that it can be carried out in the absence of facilities for cultivation of the organisms ; this obviously makes it much more widely available in tropical countries.

The dilutions are made precisely as described in the microscopical method, but after expelling the measured quantities of diluted serum and emulsion into a watch glass to mix them thoroughly, the fluid is once more made to run up the capillary tube, so as to form a long unbroken column in its upper part, and then the lower end is sealed by heat. The tubes containing the different dilutions are marked with a wax pencil and stood upright in a test tube for about twenty-four hours. At the end of this time they are carefully examined for precipitate, and it will be found if the reaction is a negative one that the whole column of fluid is still fairly uniformly hazy or opaque, as in a control tube with equal parts of salt solution and emulsion only, which should always be put up at the same time as the serum dilutions. On the other hand, a complete reaction with any given dilution will show a dense white precipitate at the bottom of the column of fluid, the remaining upper portion of which will be quite clear. Partial precipitation may indicate an incomplete reaction.

In order to get reliable results with this method it is essential that the blood serum used for making the dilutions should be free from blood corpuscles, which will fall to the bottom of the column and simulate a precipitate of the organisms. To ensure this it is best to centrifuge the serum in the collecting tube before using it, or if a centrifuging is not available the corpuscles will fall to the bottom of the blood serum on allowing it to stand for one hour before using it. In order to be sure that the precipitate in the capillary tubes is really due to clumping, at the end of twenty-four hours, when the reaction is being noted, the end of the tube should be broken off and the precipitate expelled and microscopied to see if complete clumping has taken place. With these precautions the test is a valuable one, and it is easily carried out under the ordinary conditions of practice in the tropics. The important practical point is the stage of the disease when a reaction appears of such a degree as to be of diagnostic value. Curschmann regards a complete clumping by the microscopical method in dilutions of from 1 in 60 to 1 in 100 as reliable evidence of the presence of typhoid, while Osler at the Johns Hopkins Hospital places it at 1 in 50 within one hour, also using the microscopical test. In my series the reaction

was tested in three different dilutions, namely, 1 in 20, 1 in 40 and 1 in 100, and Table XXI. shows the degree of reaction obtained at different periods of the disease.

TABLE XXI.—SERUM REACTIONS IN TYPHOID

	Negative in 1-20 dilution.			Positive up to 1-20 only.			Positive up to 1-40 only.			Positive up to 1-100.			Total Positive Reactions.		
	Total.	Rested later.	Reacted later.	Total.	Rested later.	Reacted in higher dilu- tion later.	Total.	Rested later.	Retested to 1-100 later.	Total.	Total.	Per cent of reac- tions.	Per cent of reaction to 1-100.		
First week .	6	4	3	2	1	1	4	4	16	10	62.5	25.0	
Second week .	15	13	12	7	6	40	68	53	77.9	58.8	
Third week .	6	3	3	8	2	2	20	34	28	82.4	64.7	
+ Three weeks	4	2	2	1	6	22	32	28	87.5	68.7	
Total .	31	22	20	10	1	1	24	2	2	86	150	119	79.3	53.8	

Only a small number of cases were tested in the first week of the fever, and 62 per cent gave some reaction, but only one-fourth of them up to 1 in 100. During the second week 78 per cent gave some reaction, but in only 58.8 per cent was it complete in a 1 in 100 dilution, while in one-third the reaction did not exceed 1 in 20. In the third week 82 per cent gave some reaction, and in two-thirds of it reached 1 in 100, while the figures for cases after the third week were only very slightly higher. The total figures gave some reactions in four-fifths, and up to 1 in 100 in 57 per cent. Out of 22 cases with a negative reaction at the first test, 20 gave some reaction on retesting at a later date, most of them being complete in a 1 in 100 dilution, while 3 which had reacted in the lower dilutions gave 1 in 100 ones later. These include 5 cases in which a negative result had been got as late as the third week, in one of which a negative result on the twenty-third day was succeeded by a complete one up to 1 in 100 on the thirty-seventh day of the fever, so that the failure of this test even after the third week will not allow of typhoid being excluded.

With regard to the significance of reactions in different dilutions my experience is in agreement with the authorities already quoted, for I have several times obtained reactions up to 1 in 20 dilution in cases which proved not to be typhoid, but this is very rarely the case with 1 in 40 dilutions, although they may be obtained occasionally in patients who have suffered from an attack of typhoid within the previous two or three years. On the other hand I regard complete reactions up to 1 in 100 by the microscopical method with a time limit of one hour, as almost absolute evidence of an actual attack of typhoid or immediate convalescence from one. Such reactions are exceptional in the first week of the disease, and only found by a single examination at later dates in from three-fifths to two-thirds of the cases. Reactions in lower dilutions are highly suggestive and should lead to further testing after a few days have elapsed, while any case at all resembling

typhoid in which a negative reaction is got should also be retested in five to seven days' time. It must also be borne in mind that *repeated negative reactions throughout may be obtained in undoubted and often very severe typhoid*, so that when clinically there are any good reasons for looking on a case as one of typhoid, a negative Widal should be allowed little or no weight against the clinical diagnosis. Where it is most valuable is in enabling very mild or abortive cases to be recognized and properly treated, and preventive measures against the spread of the disease being taken, but it *still remains only an additional aid in forming a diagnosis*, which in the majority of cases can be made from a study of the temperature curve, pulse rate and other clinical characters before a reliable Widal reaction can be obtained.

The Widal reaction is a less simple and reliable proceeding in the case of patients who have been inoculated against enteric with the *B. typhosus*, producing agglutinins in the blood, which persist for a variable period. According to Wade and McDaniel one year after inoculation only 11·7 per cent gave positive Widal reactions, while Dyer working at Kasauli concluded that six months after injection reactions of 1 in 40 and over indicated the presence of typhoid fever, and Baker at Haslar, as a result of over 1000 tests in patients from Gallipoli, found that one to one and a half years after inoculation only 20·8 per cent gave reactions as high as 1 in 50, and after only six months a positive reaction up to 1 in 250 is necessary for diagnostic purposes. Levy in Paris found that in healthy inoculated subjects the agglutination with *B. typhosus* is nearly always under 1 in 300, and that reactions in dilutions 1 in 200 with *B. paratyphosus B* and of 1 in 50 with *paratyphosus A* were diagnostic of those forms of enterica. Courment Chattot and Pierret have especially studied serum tests for paratyphoid and disregard all reactions of less than 1 in 50 for *B. paratyphosus A* and of under 1 in 100 for the other two forms. From a comparison of positive blood cultures with serum tests in 109 cases they concluded that reactions in those dilutions were reliable in uninoculated persons, but after inoculation with Eberth's typhoid bacillus it is of no value if occurring concurrently with paratyphoid reactions. Positive paratyphoid A reactions are most reliable, while those with paratyphoid B are valuable if in considerably higher dilution than with the *B. typhosus*, irregular or paradoxical reactions having been met with in only three cases, or 2·8 per cent, in two of which a repetition of the test cleared up the case. Thus the serum test alone sufficed to clear up 78 per cent of their cases.

Latham has described a rapid bedside method in which four drops of a 1 per cent formalin solution of 10,000 million dead bacilli in a c.c. is added to one volume of serum and three of water on a slide and well mixed. In two minutes clumping is visible with the naked eye if the reaction is positive.

Dreyer and his colleagues have worked out a method in which standard Oxford dead cultures are used, and a series of dilutions made in small test tubes with all three varieties of *B. enterica*, the readings being made in a cupboard with a black background and an electric lamp. Glynn and Lowe after making about 3000 tests found the plan simple and reliable, and it has been largely adopted. More blood is required, but can be taken in large Wright's capsules. Simultaneous agglutination with paratyphoid A and B only occurred three times in 600 sera and in two of these paratyphoid vaccine had been used. Paratyphoid A reactions are reliable in much lower dilutions than B, Dryer stating

that even a 1 in 10 paratyphoid A is diagnostic. Now that mixed triple vaccines are being extensively used among military forces the serum diagnosis will be still more difficult, and such a standardized method as Dryer's is likely to be necessary to enable reliable results to be obtained.

Anaemia of a mild degree is produced by typhoid, but is not a very marked clinical feature, nor is it of any diagnostic importance.

Changes in the White Corpuscles are of greater significance. In the first place there is a progressive decrease of the total number of the white corpuscles in the course of the disease, and leucocytosis never occurs except as a result of such complications as pneumonia, periostitis and other inflammations.

The Differential Leucocyte Count is also of considerable importance in typhoid in the tropics. Table XXII. gives the variations in both the lymphocytes and the large mononuclears in a number of cases in which the counts were made by me. The most

TABLE XXII. DIFFERENTIAL LEUCOCYTE COUNT IN TYPHOID

	Up to 8 per cent.		8-11 per cent.		11-15 per cent.		Over 15 per cent.						
<hr/>													
I. Percentage of large Mononuclears.													
Cases	86		9		10		8						
Percentage	76.2		7.9		8.9		7.0						
<hr/>													
Up to 30 per cent. 30-40 per cent. Over 40 per cent. Total.													
<hr/>													
II. Percentage of Lymphocytes.													
First two weeks	25	52.1	15	31.8	8	16.6	48						
After second week	18	37.5	11	22.9	19	39.6	48						
<hr/>													
.	43	44.8	26	27.1	27	28.1	96						

important point to note is that a marked large mononuclear increase was very exceptional, while, on the other hand, the lymphocytes may be frequently present in considerable excess, in proportion to which the polynuclears will be reduced. Thus, in 76 per cent of the examinations the large mononuclears did not exceed the normal rate of up to 8 per cent, while in 8 per cent more only from 8 to 11 per cent were present. In 9 per cent they numbered from 11 to 15, and in only 7 per cent did they exceed 15 per cent. On comparing these figures with those for malaria and kala-azar on pp. 254 and 41, it will be seen that typhoid shows a large mononuclear increase in a much smaller percentage of the cases than the latter diseases, and usually only late in its course. Moreover, several of the cases in which this increase was found were complicated by malaria, the parasites of that disease being found in the blood in addition to the serum test, although

the complication had little effect on the temperature curve except in convalescence, as already mentioned (see p. 109).

In over half the cases the lymphocytes exceeded the normal upper limit of 30 per cent, while in 28 per cent they exceeded 40 per cent. The increase was, however, less marked during the first two weeks than later, so that it is not found in quite half the cases during the earlier periods of the fever. The lymphocyte increase is commonly absent in the most severe cases, while it is as a rule very marked in the milder forms, in which its presence, without any large mononuclear increase, is often an important indication of the presence of typhoid rather than that of malaria or kala-azar, but similar counts are frequent in seven-day fever, in which this test is of very little help.

On the whole the differential leucocyte count is not of as much practical value in typhoid as I had at one time hoped would prove to be the case, although the absence of any large mononuclear and large lymphocyte increase is a point of considerable diagnostic importance in favour of typhoid as against early kala-azar, and one which has often proved of great service in actual practice.

Cultivations of the Typhoid Bacillus from the Blood.—Where a laboratory is available a still more certain and early test of the presence of typhoid fever may be carried out by taking several cubic centimetres of blood from a vein, and diluting it in several hundred cubic centimetres of sterile broth. In this way the typhoid bacillus may be obtained in pure culture in a large proportion, for out of 604 cases collected by Coleman and Buxton in New York, in 75 per cent positive results were obtained. During the first week of the disease the typhoid bacillus was cultivated in 93 per cent, in the second week in 76 per cent, in the third week in 66 per cent, and in the fourth in 32 per cent. The great advantage of this test, when it is available, is that *positive results are said to be obtainable as early as the second day of the fever*. Up to the seventh day positive results are usually obtained, but after the tenth day blood cultures are only occasionally successful, but by this time the serum test will be available. In inoculated subjects, in whom the Widal test is less simple, blood culture is by far the most reliable diagnostic method when the patient is seen early enough; while later cultures from the stools or urine may be successful in isolating the causative bacillus whether that of true typhoid or a paratyphoid. The table showing the incidence of paratyphoids on page 93 gives the results of blood culture for all forms in several considerable series of cases.

Various forms of culture media have been recommended, but the main points to bear in mind are either to use ox bile to favour the growth of the organisms or greatly to dilute the blood to lessen its bactericidal action on the bacilli. The original method of adding 5 to 10 c.c. of the patient's blood to 5 c.c. or more of ox bile, and, after incubating for about twenty-four hours at 37° C., sub-culturing in broth, is very reliable. When fresh ox bile is not available the blood may be added to fifty times as much broth, or better 2 per cent taurocholate of soda in water may be used, and after incubating at blood heat for a day plant out on McConkey's plates daily for four days and test the isolated colonies, as advised by Archibald and others. Blood taken by puncturing a sterile finger-tip may suffice for making successful cultures, especially in severe cases, the broken-up blood-clot being used for the purpose.

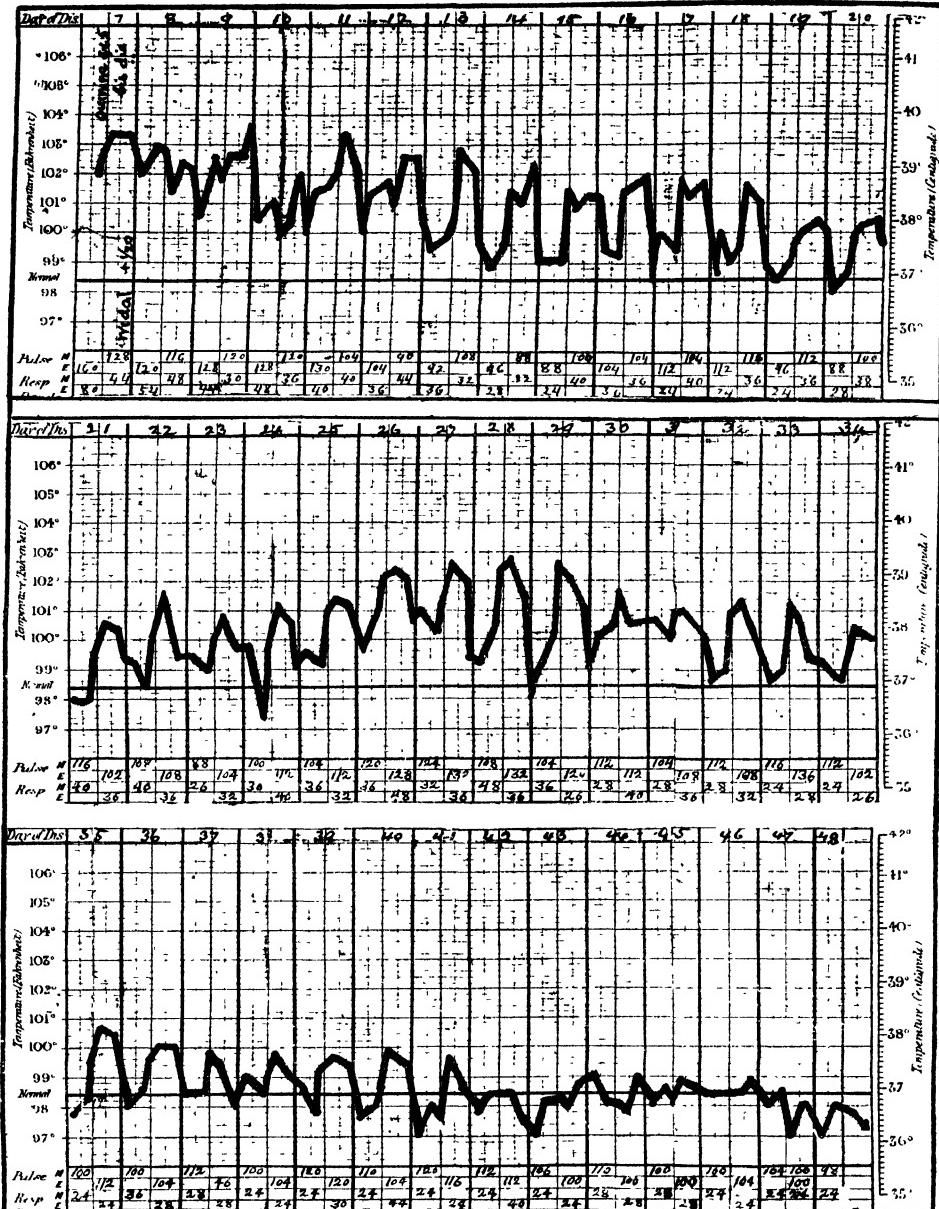
Treatment.—The clinical identity of typhoid in India, with that of temperate climates, makes it unnecessary to say much in this work on the treatment of the disease, which should follow well-known principles. In the European Hospital at Calcutta chlorine mixture with 3-grain doses of quinine has been used systematically in the great majority of typhoids, but the long average duration already noted proves that it in no way shortens the attack, while some cases treated by me in the same hospital without any systematic drugging, but only occasional measures for the relief of special symptoms, did at least equally as well as those taking the very unpleasant chlorine solution. Some cases which were at first thought to have been typhoids cut short by the chlorine treatment proved afterwards to be only seven-day fever.

Cold Applications.—Measures directed towards preventing the temperature remaining persistently at a very high level are of special importance in the tropics, where for so many months in the year the atmospheric conditions are such as to favour the sudden supervention of hyperpyrexia. Some years ago very depressant drugs of the antipyrin type were largely used for this purpose, but happily this has been almost entirely given up at the present time in favour of cold applications, which have the all-important advantage of acting as cardiac tonics as well as refrigerants. The precise method of applying cold is more difficult to decide, as the results obtained by the cold-bath treatment in Australia by Hart are very striking, while F. K. Newland, R.A.M.C., treated 111 cases of enteric at Quetta by this method with a mortality of 17 per cent. The great difficulty in carrying out this treatment in the tropics is the want of the amount of skilled assistance to enable it to be safely used in the large number of cases which have to be dealt with. Moreover, very good results are obtained by the long-continued application during the persistence of high temperature of sheets wrung out in cold water, which plan obviates the danger of moving the patient into and out of the bath. In Calcutta, and most places in the tropics, this cold-pack treatment is generally used, and on the whole it appears to be the best for adoption under ordinary circumstances. Cold-air baths may also be used by placing ice in a tray suspended from a cradle under the bedclothes.

The Regulation of the Bowels.—The frequent occurrence of persistent constipation in typhoid necessitates the frequent use of enemas to empty the large bowel. The common routine use of a purgative on the admission of patients to some hospitals for any kind of fever may lead to disaster if given in an unrecognized typhoid case, to meet which it is a rule in Calcutta that no purgatives may be ordered by a subordinate medical officer for a fever patient until he has been seen by the physician in charge of the ward. Excessive looseness of the bowels may require to be checked by opiates in small doses, which, given with due care, are of special value in this class on account of the danger of haemorrhage or perforation.

Haemorrhage from the bowels is the most frequent serious complication of typhoid, and has to be considered both as regards prevention and treatment. When it occurs within the first two weeks and is not copious enough to affect the temperature and pulse, it usually does little harm, but should it come on at a later date and produce a marked fall of temperature and quickening of the pulse the life of the patient is in immediate danger.

CHART 24 (Case 1144)



Prolonged low remittent and intermittent fever. Widal positive 1 in 20 only on eighth day, negative on twenty-second day. Pelvic trouble suspected as cause of fever and operation proposed. Typhoid bacillus cultivated from the blood on twenty-ninth day.

In addition to the usual treatment by opium to rest the bowel, and by cold applications to the lower abdomen, drugs which increase the coagulability of the blood are indicated. The most rapid of these is undoubtedly calcium chloride, which should be given at once in a dose of 30 grains, and repeated after four hours, but not more than two or three doses should be given lest the negative effect of reduced coagulability due to pushing it be produced. After a day or two it can be repeated if necessary. Another drug, of perhaps even greater value in this condition, is turpentine, which I showed some years ago produces some general increased coagulability of the blood in addition to its powerful local haemostatic action, so that it would appear to be an ideal medicine in the treatment of intestinal haemorrhage, and yet it is not used as much as it ought to be for this purpose. It must be given in at least 15-minim doses, best in capsules to prevent it being tasted. In several very critical cases, after the failure of all other treatment, the use of this drug has been followed rapidly by final cessation of the malaena and recovery of the patient. Subcutaneous injections of horse serum (an out-of-date anti-diphtheritic or anti-dysenteric serum may be used) in 10- to 20-c.c. doses are also of great value, while in an urgent case these might be given intravenously with due precautions regarding anaphylaxis.

The prevention of haemorrhage from the bowel depends on the early recognition of the reduced coagulability of the blood on which Wright states it depends. The fact already pointed out (see p. 120) that the more serious class of haemorrhage from the bowel almost always occurs during the third and fourth weeks of the disease, and the great majority of cases of haemorrhage have had marked or persistent diarrhoea, indicates routine testing of the coagulability in this class of case. If the blood takes more than five minutes to clot with Wright's tubes steps should be taken to increase the clotting power of the blood and their effects carefully watched. Here, again, a warning against the prolonged use of calcium chloride must be given, for although increased clotting is produced within about fifteen minutes by this drug, after a few doses it must be left off for a day or two, lest the opposite negative result be produced, and haemorrhage may be actually caused instead of being prevented; this actually happened in one case in which this precaution was neglected and the drug continued for a number of days.

The opposite effect of increased clotting, leading to thrombosis in the late stages of the disease, may also be watched for, and such precautions may be taken as decalcifying all milk given by the addition of a little citrate of soda, or the internal administration of citrates. This citration of the milk also has the great advantage of making it clot in the stomach in very much smaller curds than untreated milk does, but in view of the frequent haemorrhages in cases of typhoid with persistent diarrhoea the loss of the calcium salts that the addition of citrates brings about may prove a disadvantage in that class of typhoid fever.

Marked distension of the abdomen is both a distressing symptom and one which may be dangerous from interfering with the action of the already weakened heart. Oil of cinnamon has recently been advocated for its relief, and very good results have followed its use in Calcutta in such cases.

The heart requires to be most carefully watched in typhoid in the tropics, where the prolonged atmospherical heat causes additional stress on this vital organ. If the first sound becomes shortened, cardiac stimulants, such as strychnine, strophanthus and,

in small and carefully watched doses, digitalis, may be of great service, while in severe cases alcohol is generally also indicated.

Quinine in small doses, such as 3 or 4 grains several times a day, appears to be the only drug of general value in controlling to some degree the temperature, and affording a mild tonic effect. If malaria complicates typhoid it may be given in 10-grain doses with 5 minimis of liquor strychninae two or three times a day for a few days only.

The Vaccine Treatment of Typhoid Fever.—Extensive trials have been made of subcutaneous and even intravenous injections of typhoid vaccines in the treatment of the disease, with such variable results that the method cannot be said to be yet established on a sure footing. Several workers, such as Reiter, Caronia and Macarthur, have recorded favourable impressions of their use of the first in small series of cases, these impressions being usually based on the fact that the temperatures have occasionally fallen rather rapidly after the injections, but these were commonly mild cases. Others, such as Lemnaski in Tunis and Deutsch, have noticed no benefit from the treatment. Rathery and Michel treated 177 cases with the vaccine, with a mortality of 3·40 per cent, and 279 without, with a death-rate of only 2·15 per cent, but as mild cases were not treated with the vaccine they were pleased with the results, the temperature frequently falling after three or four injections. Whittingdon treated 230 cases, half with a stock vaccine, while the other half were kept as controls, and he noted that favourable results were obtained in comparatively mild cases, which would have done well under any treatment, but the method failed in severe ones. He concluded that the treatment was of very doubtful efficacy, while there was a decided suspicion that it predisposed to haemorrhage. A living vaccine has been used by Bourke, Evans and Rowland with apparent benefit. Sensitized vaccines after Beredka's method have also been tried, and Echikawa in Japan claims to have aborted typhoid fever by the use of a typhoid vaccine sensitized with the serum of convalescent patients. Ten loops of a young typhoid culture were incubated at 37° C. in 10 c.c. serum for five or six hours, washed in salt solution and suspended in 100 c.c. saline with 0·3 per cent carbolic, and 0·5 c.c. injected slowly into a vein and repeated if the reactionary rigour was not followed by a rapid and lasting fall to normal. In 87 cases he had a mortality of 11 per cent against a previous one of 30 per cent in the same hospital. He also noted a tendency to haemorrhage after the injection, but it was never serious. Szecsy also used Beredka's vaccine in army cases, many being wounded, and his mortality fell from 22 to 2 per cent. He obtained the best results with a vaccine not more than 12 days old, containing half-a-loop of sensitized bacilli in each c.c., and gave 1, 2, 3 and 4 c.c. on successive days. He had 25 per cent of relapses, which yielded to a further dose of 4 c.c. The duration of the disease was reduced to 8 to 10 days. This method is based on the sound principle of first removing the toxicity of the injected cultures and appears to be worthy of further trial.

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IV. TYPHUS FEVER AND TYPHUS-LIKE FEVERS

I. TYPHUS FEVER

Geographical Distribution.— Typhus fever is still endemic in Ireland, the north of England and in the Hebrides, in Poland and Galicia and parts of Russia, Turkey and the Balkans, in Spain and in Europe; in Northern Africa, especially in Algeria and Tunis; while in the Western Hemisphere its main seat is in Mexico, although Goldberger states it is also endemic in several large cities of the United States. Owing to war conditions numerous outbreaks have occurred in Servia, Austria and Germany, chiefly in prisoners' camps, and it has also been seen in Palestine. In Africa it has also been reported by Sandwith in Egypt, while Balfour states that it was prevalent in the Soudan in Baker's time about 1864, but has not been seen since the reconquest. Foster has reported cases in the Philippines. During the Japanese-Russian War cases resembling typhus occurred in Manchuria. In America, in addition to its home in Mexico, the disease has been reported in New York, in Georgia, New Mexico and Texas.

There has been much difference of opinion among older writers on the question as to whether true typhus fever occurs in India or not. The terrible annual death-rates of 200 and upwards per thousand which used to occur in the insanitary and overcrowded jails of the Punjab, even as late as 1878, were attributed, by some experienced medical officers, and apparently with good reason, in part, to the prevalence of typhus fever, De Renzy having seen several outbreaks in which medical officers caught the infection. On the other hand, Norman Chevers in 1886 held with Morehead and Murchison that proof was still wanting of the existence of genuine typhus in India, although a number of cases considered to be typhus had been recorded in various parts of India, and he points out that in some of these instances the descriptions of the outbreaks more closely resemble relapsing fever, the outbreak in the Yusufaie Valley north of Peshawar being a case in point.

Coming to more recent times the following outbreaks of the disease have been reported, all of them from the Punjab. In 1892 L. J. Pisani, I.M.S., while in charge of the coolies working on the Chaman extension railway in Baloochistan, saw many fever cases which he attributed to the prevalence of both relapsing and typhus fever, the diagnosis of the latter disease being based on the facts that in one place forty out of forty-five died and in another the mortality was 40 to 50 per cent, while 6 cases were seen with a dusky rash, which clinically more closely approached to typhus than anything else. In view of the typhus-like cases of relapsing fever which have been reported in India by Vandyke Carter

and quite recently by McCowen it seems to be possible that all Pisani's Chaman Railway cases were relapsing fever without the addition of true typhus.

In 1894 the same writer returned to the subject in the *Transactions of the First Indian Medical Congress*, and after referring to the numerous outbreaks in jails described by Bryden in his statistical reports, he states that there is an endemic area in the north-east of India, including the Trans-Indus districts from Baluchistan to Ensufzai, the Hazara and Rawal Pindi districts and the Himalayan hill tracts. In addition to the outbreak just referred to, he also describes one in the Hoti Madan lock-up from April to June 1888, during which he saw 9 cases with fever of fourteen to nineteen days' duration with a distinct morbilliform purplish rash in 8 of these. Infection was shown by two constables on guard being attacked, while the fever was also carried to the Peshawar jail in February 1889, where 47 cases with 7 deaths occurred.

In the same publication W. Vost, I.M.S., who had previously seen typhus in Glasgow, recorded an outbreak of the disease in Baluchistan among coolies between December 1892 and April 1893, beginning during cold weather when the men huddle closely together, several cases frequently occurring in the same tent. The fever was of a continued type from 102° to 104.5°, and lasted from thirteen to fourteen days, usually terminating by lysis. Five deaths occurred among 18 cases in hospital.

R. Hendley, I.M.S., also dealt with this subject at the same Congress, and had no doubt about the occurrence of typhus in the Punjab, having notes of 53 cases in the Peshawar Valley outbreak in 1891-92, the distinguishing features of the disease being unmistakably marked in the majority of the cases. It spread down with the traffic in the spring from Afghanistan, attacking villages on high ground in not particularly malarial districts, spread rapidly in families, few of whose members escaped an attack, and also infected two persons by contact in the Peshawar jail. The incubation period in severe cases was five to seven days, but somewhat longer in the milder ones; the rash usually appeared on the fifth or sixth day, being well seen in the light-skinned Pathans; it became petechial in the later stages, and was confined to the chest, abdomen and inner sides of the arms, resembling measles except that it was not crescentic. The temperature generally rose within the first forty-eight hours to 102° or 103°, and by the fifth day reached 104° or 105°, varying from $\frac{1}{2}$ to 1° in the twenty-four hours, usually falling a degree or two when the rash appeared, and then becoming continued again, but at a lower height than at first, and terminating by crisis generally on the fourteenth day, but occasionally not until the twenty-first day, while in fatal cases death took place from the seventh to the fifteenth day. Among the symptoms noted were suffusion of the conjunctiva, thickly coated tongue tending to become dry, congestion of the lungs, with sometimes pneumonia and constipation. Post-mortems showed an absence of typhoid or other specific lesions. An outbreak 50 miles from Simla is also referred to by this writer. He states that in the nine outbreaks in the Peshawar jail the disease always ceased in April with one exception, when it terminated on May 20, thus dying out with the onset of the hot season.

The above outbreaks, taken with the frequent occurrence of severe epidemic fevers in the Punjab jails at earlier periods, leave no doubt that typhus fever does occur in the north-east of the Punjab, although with the recent great improvement in the sanitation of Indian jails, it now seldom comes under close medical observation.

In 1908 Husband and MacWatters reported cases in the Punjab, and pointed out that they have been mistaken for epidemic pneumonia, while Hepper also saw cases in the same year at Peshawar.

Etiology.—During the first two decades of the twentieth century great advances have been made in our knowledge of the causation and mode of transmission of typhus fever, which should make it easier to stamp it out once normal conditions are restored in Europe. The **bacteriology** of the disease has engaged the attention of many writers, and the extensive researches of Plotz of New York have gone far towards placing the *Bacillus typhi-exanthematici* on a firm basis as the causative organism of the disease. Numerous previous workers have described very similar organisms, notably M. Rabinowitsch as early as 1908, Wilson in Belfast in 1910, Fuerth at Tsingtu, Muller of Trieste (1913), while Hort and Ingram also mention Dubieff and Bruhl as among the first to find it. In May 1914 Plotz published his first account of the cultivation of the organism grown from the blood of both Brill's disease and typhus, and in July Hort and Ingram found the same organism, but did not regard it as the cause of typhus, but attributed that rôle to a smaller organism which they did not succeed in growing. In 1896 Penfold described cultures of Gram-positive cocci which produced infection in monkeys, but which he thinks differs from Plotz's diplo-bacillus. In 1914 Sergent, Foley and Ingram and Vialatte found very similar bipolar staining cocco-bacilli in the organs of lice fed on typhus patients, not in control uninfected insects. Plotz's organism is strictly anaerobic and grows best on serum-glucose-agar, but so slowly that it is of little diagnostic value in an individual case, because the fever has usually ceased before a culture is obtained. Paneth with a different medium found the earliest colonies appeared on the fifth day, most from the tenth to the twelfth day and some up to twenty-one days. The organism is a small non-motile Gram-positive bacillus varying in length from 0·9 to 1·93 microns, its breadth being from one-fifth to three-fifths of its length. Degeneration and involution forms appear early. The organisms are most abundant in the blood of patients on the fourth or fifth day before the crisis, and the number present is in relation to the severity of the infection. Serological, agglutination and complement fixation reactions have been demonstrated with the organism. The serological reactions may be of diagnostic importance as they were obtained in 16 cases of typhus in which bacteria were not obtained from the blood. The organism has been recovered from the blood of animals infected with the disease by the inoculation of typhus blood. A good case therefore appears to have been made out for this organism being the cause of typhus.

Infection of Animals with the blood of typhus patients, and more recently with the bacillus cultivated from cases, has frequently been obtained. In 1910 Nicolle infected a chimpanzee with the blood of a typhus patient, and also a bonnet monkey from the former, and in the same year Ricketts and Wilder conveyed the infection of Rocky Mountain spotted fever to guinea-pigs. In 1912 Anderson and Goldberger also infected monkeys and guinea-pigs. In 1913 Rabinowitsch infected guinea-pigs both with the blood of typhus patients and with a diplo-bacillus he had cultivated from them, and also rabbits and two pigs. In 1915 Nicolle reported repeated passages of the virus through monkeys and guinea-pigs through the bites of infected lice, and also infected rabbits experimentally.

In one case he found infection in a new-born guinea-pig whose mother had been inoculated with typhus ten days before, showing hereditary infection.

The Transmission of the Infection by Lice has been firmly established, while, as it is doubtful if any other mode of infection occurs, this fact is of the utmost practical importance. Nicolle, working in Algeria, was the first to establish this experimentally in 1909, but it appears that Cortezo as a result of his experience of typhus in Madrid suggested lice as the probable carriers at the Paris Sanitary Conference of 1903, but long before in a Report published as early as 1817 Krantz mentioned the relation between lice and typhus, the disease having been epidemic in Eastern Europe during the Napoleonic wars. Nicolle found that lice fed on the blood of typhus cases in the febrile stage were effective in transmitting the disease by their bites from the fifth to the seventh day subsequently, while their body-fluids were also infective. Later he concluded as a result of much further work that fed lice were not infective before the eighth day, while the ninth and tenth days were the most effective. Comte and Conseil in North Africa, Sergent, Foley and Vialatte in Tunis, Ricketts and Wilder in the Rocky Mountains, and Anderson and Goldberger in New York all obtained infection through lice, but the hereditary transmission through these insects has not been fully demonstrated. Olitsky has shown that the virus is non-filterable.

The Incubation period was found by Nicolle in guinea-pigs to be usually from 8 to 11 days, but to extend from 5 to 21 days, and by Anderson and Goldberger experimentally in monkeys to be from 6 to 10 days, and the duration of the fever 6 to 11 days. Juergens in a Russian prisoners' camp put the incubation period of typhus at between 2 and 3 weeks, Cadwell and Howell in Servia respectively concluded that it was 11 and 14 days.

The Prophylaxis of typhus fever is summed up in the destruction of lice. The whole history of the disease is in agreement with the infection being carried by an insect so closely associated with poverty, filth and overcrowding. Vagrants have frequently introduced infection into places, while the deficiencies of cleanliness and sanitation incident to reversion to the semi-barbarism of wars led to severe outbreaks of the disease in the Napoleonic, Crimean, Russo-Turkish, and Balkan wars, as well as in Eastern Europe during the world conflict of the twentieth century due to a recurrence of the dynastic and racial ambitions of a century ago. The practical value of a knowledge of this mode of transmission is well seen in the results of prophylactic measures based on it in Tunis, where Conseil reports that the number of cases of typhus has steadily fallen year by year from 836 in 1909 to only 3, all imported cases, in 1914. All workers are agreed as to the principle, but very various measures which require to be discussed under different headings have been recommended for the purpose.

Personal Prophylaxis is most required in the case of nurses, doctors and other attendants on typhus patients. In the first place, special clothes have been recommended in the form of louse-proof linen or cotton under-garments made in one piece from the feet to the neck, opening in front or combined with Wellington boots, together with a cotton cap (Merewether and Howell). Five per cent naphthalene, either as a powder or an ointment, may be applied at the opening in the neck by being dusted or smeared on, or

bags of the powder worn there. Masks worn over the face to prevent infection from droplets of mucus or saliva sprayed by the patients has also been suggested, but it is doubtful if this is necessary, as Goldberger failed to produce infection in animals by inoculating them with buccal and pharyngeal secretions. A 15 per cent alcoholic solution of anisol has been advised for applying to the body for keeping off lice, or 1 of mercury perchloride in 300 of vinegar, or 10 per cent salicylic acid. The following Russian receipt may be used : crystallized phenol 1, naphthalene 1, petrol 9, and Russian turpentine 9 parts, kills both the insects and their eggs (including bugs and fleas as well as lice), and has been found effective for disinfecting rooms, being sprinkled on floors, beds, etc., twice a month.

For Disinfection of Patients to kill lice on them and their clothes the following methods have been advised : cresyl, either as a 2 per cent by volume mixed with water or as a 5 per cent soap for washing patients and their clothes, 5 to 10 minutes' exposure of the latter being sufficient, the clothes then being washed ; 10 per cent camphorated oil, 15 per cent oil of turpentine, 10 per cent camphorated spirit, 5 per 1000 chloroform water, a solution of anisol, 5 c.c. with 50 c.c. of 90 per cent alcohol and 45 c.c. water ; which give a varied choice to suit individual tastes. Two spoonfuls of sulphur precipitatum well brushed into a woollen shirt is also said to keep off lice for at least two weeks. For disinfecting clothes, bedding, etc., on a large scale 7 per cent of sulphur dioxide gas for four hours is necessary, while formalin is said to be less effective. A steam sterilizer is also effective, dry heat being better than moist.

CLINICAL DESCRIPTION

The Onset of the disease is sudden, with few prodromal symptoms beyond weakness and headache. The incubation period was found recently in the Balkans to be usually from 10 to 12 days, but may be less, and in Mexico, Hall found it to vary between 5 and 15 days. The first symptoms are severe headache, pains in the body, prostration, and a rapid rise of temperature to from 101° to 104°, while it may continue to rise with slight morning remissions for another 2 or 3 days, and then run a continued or high remittent type to from the tenth to the twelfth day in typical cases, falling as a rule by crisis, but occasionally by lysis. Before the crisis the patient usually has reached a very bad condition with very low blood pressure, severe nervous symptoms with drowsiness and delirium, ending either in death or rapid convalescence after the critical fall in temperature.

The Rash usually appears on the body on the fourth to the sixth day, but most frequently on the fifth day, sometimes beginning with an erythema, but rapidly becoming macular and spreading to all parts of the body except the face, palms of the hands and soles of the feet. Later it often becomes petechial, when it is more visible on a dark skin than the macular eruption. Dietsch showed that artificial stasis, by means of a tourniquet applied round the upper arm for from half to one minute, causes the exanthem to become visible in cases in which it is not characteristic, so this plan may be of diagnostic importance. Congestion of the conjunctiva, sometimes seen as bands running from the

inner canthus to the cornea, is an early and characteristic symptom, and may give the patient a drunken appearance.

The Tongue early becomes thickly furred, dry and cracked, while the edges are red. Difficulty in putting out the tongue is said to be an early diagnostic sign.

The Blood changes are fairly characteristic, a polynuclear leucocytosis being nearly always present in the earlier stages before the rash appears, while the eosinophiles disappear. Later, if the patient is doing well, the proportion of polynuclears may decrease and of the mononuclear increase.

Variations from the typical condition occur in the form of rare fulminant cases dying before the rash appears, and more common mild cases presenting difficulties in diagnosis unless accompanied by typical cases as is usual. In children the disease is much milder than in adults, while infants under one year nearly always escape and children of from 1 to 7 years are seldom attacked. With every decade the mortality rises, so that in persons over 40 years of age the disease becomes much more dangerous. Thus Molodenkoff recorded 115 cases in children of from 1 to 14 with no deaths.

The Mortality is very variable, being sometimes as high as 30 to 40 per cent or more, especially under unfavourable war conditions, while at others it is only about 11 per cent. Outbreaks are generally more severe in the winter.

Complications are not very frequent, rapid regain of strength after the crisis being a prominent feature of the disease, although the heart remains weak for some days, and the recumbent position should be maintained for a week after the temperature becomes normal. The most frequent complications are broncho-pneumonia, otitis media with deafness, myocarditis, parotitis, and dry gangrene due to arteritis, while neuritis, hemiplegia and meningitis have also been recorded.

Diagnosis.—In addition to the clinical points already mentioned certain agglutination reactions have been recommended as of diagnostic value. As early as 1910 Wilson showed that both a *B. coli communis* from the stool and an organism obtained from the urine of two cases, which belongs to *Proteus vulgaris* group, were agglutinated in dilutions up to 1 in 100 by the serum of typhus patients, but not by normal serum. Several years later two German workers, Weil and Felix, obtained similar results, and their compatriots have called the test by their names, ignoring Wilson's much earlier work. This reaction is said to be positive in about 90 per cent of typhus cases, although it is a heterologous agglutination, the *proteus* organism not being the cause of typhus. Anderson recommends the injection of 3 or 4 c.c. of the blood of doubtful cases into guinea-pigs or monkeys, and plotting out the temperature curve obtained by taking the rectal temperature twice daily for three weeks. Baehr has demonstrated agglutinins against the *B. typhi-exanthematici* in 93 per cent of typhus cases, while non-typhus ones gave uniformly negative results.

Treatment.—This is mainly symptomatic, although there has recently been some promise of more directly curative measures becoming available. In addition to the usual methods of treating fevers by supporting the strength with liquid nourishment

and careful nursing, salines are of value in flushing the system and removing toxins. Many authorities, including experienced Servian doctors, consider alcohol should be prohibited, but others use it as a stimulant. Open-air treatment has been frequently advocated for the benefit of the patient, while it may tend to lessen the infection, although of much less importance in this respect than cleanliness as regards lice. Cold baths, urotropine, quinine in repeated small doses, peroxide of hydrogen to combat oral sepsis, digitalis, strychnine and caffeine for weakness of the heart, lumbar puncture with removal of 10 to 20 c.c. of fluid to relieve the nervous symptoms have all been recommended by experienced physicians as of value in typhus. Salvarsan has failed to afford any benefit. More directly curative action has been claimed for colloidal gold and silver injected intravenously. Bouygues found 1-c.c. doses of gold collobiasis to be followed by a rigor and profuse sweating, tachycardia and subsequent great improvement in serious cases. Repeated intravenous injections of "fulmargin," a silver colloid preparation, are also reported favourably on. Of still greater interest and promise is the **serum treatment**. Nicolle first showed that the serum of patients convalescent from typhus possesses immune substances which protect animals against typhus infection, and he and others have reported very favourable results in typhus cases from the injection of 10-c.c. doses of such serum. Both Nicolle and Plotz have made antitoxic serums by injecting cultures of the typhus bacillus into asses and horses, and several trials have been made with promising results. Thus Nicolle advises 10 c.c. daily, and reports 19 severe cases with rapid recovery in all the early ones and slower improvement in the later ones. With further experience this method seems likely to prove of great value as a specific curative treatment of this deadly disease.

II. TYPHUS-LIKE FEVERS

In widely separated places typhus-like fevers have been recorded under various names, which have been mostly shown to be insect-borne. The following are the most important of them.

Rocky Mountain Spotted Fever is endemic in the Montana and Idaho districts, the disease having a much higher mortality in the former than in the latter, and also in the Modoc and Lassen countries of California. It was proved by Ricketts that the infection is carried by the bites of ticks, both *Dermacentor venustus* and *D. modestus* having been incriminated. Guinea-pigs and white rats are readily infected, and Wolbach found diplo-bacilli, especially in the muscular wall and endothelial cells of blood-vessels and lymphatics of guinea-pigs and in ticks in striped muscle, the salivary glands and ducts, Malpighian tubes, brain ganglia and in the muscle of the uterus and vagina. The infection is also hereditary in ticks. Fricks in Montana cultivated anaerobically diplo-bacilli similar to those Plotz found in true typhus, and also infected guinea-pigs from three-week-old cultures. The sediment of centrifuged blood serum from cases also infected animals. The virus is non-filterable. Ticks are not infective until twenty-four hours after feeding on infected animals. Fricks also found that Rhesus monkeys can be infected, and that six species of wild rodents are dangerous tick carriers and should be

destroyed. King incriminated ground-squirrels, while Parker states that 60 per cent of jack-rabbits harbour ticks.

Mickie and Parsons describe the disease as commencing suddenly with continued fever, pain in the head, back and joints, slow pulse, early enlargement of the spleen, albuminuria and a typhus-like eruption. They found atoxyl and salvarsan worse than useless, and advise 60 c.c. of 5 per cent sterile fresh sodium citrate solution intravenously.

The prophylaxis consists in the avoidance of the bites of ticks, dipping horses and cattle into solutions to kill ticks, and the destruction by poisoning or shooting of ground-squirrels and rodents which harbour infected ticks. One attack produces immunity.

Japan River Fever, Kedani Disease or Tsutugamushi, occurs in the northern parts of Japan as a serious typhus-like fever with a mortality of from 20 to 50 per cent, and has also been met with in Formosa. The infection is carried by a small mite, the Lepto-thombidium akamushi, and marmots have been infected experimentally. The larval form of the mite conveys the disease. The causative organism has not yet been definitely established, but the disease is believed to be closely allied to Rocky Mountain spotted fever, and to a series of cases described by Schueffner as **pseudo-typhus** at Deli in Sumatra, in which the infection is probably conveyed by a tick or a mite, and is characterized by necrotic ulcers at the site of infection, roseala rash and fevers for 8 to 10 days rather resembling typhoid. A similar disease has been recognized in the Philippines by Ashburn and Craig, and isolated cases reported by Dowden in the Malay States and Weir in Korea.

In **Africa** Conor and Bruch have met with a similar fever in Tunis, which they described in 1910 as "Macular Fever," while Gabbi saw it in Tripoli, Balfour at Khartoum and MacNaught in South Africa.

In India Megaw recorded two cases resembling Brill's disease from the Kumaon Hills in the United Provinces Himalayas, where relapsing fever is also endemic, and he discusses the relationship of the above fevers.

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V. RELAPSING FEVER AND AFRICAN TICK FEVER

RELAPSING fever due to a spirillum in the circulating blood is a very widely distributed disease, being found in Eastern Europe, India, and other parts of Asia, America and Africa, different varieties of the disease with organisms to which distinct names have been given having been described on each of these continents. The Central African form due to *Spirillum duttoni* is clinically quite distinct from the other forms, and will be described separately. On the other hand there is considerable doubt regarding the specific characters of the minute distinctions which have been described between the other three varieties, and even about the facts regarding the important cross serum reactions. Thus, while Mackie holds that these three forms can be distinguished by the serum reactions, Strong after careful tests failed to confirm this view, and concluded that the Bombay spirillum fever is very closely related, if not identical with, the forms of relapsing fever met with in Europe and the United States, although distinct from African tick fever. On the clinical side Chowsky has published a table showing the differences described in the symptomatology of the different forms, but a close examination of it reveals most striking resemblances and only minute differences, and completely fails to afford any clear distinctions between the European, India and American forms, although these three differ materially from the Central African form. In Egypt and North Africa yet another variety has been described as due to the *Spirillum berbera*, which differs from the African tick fever, but resembles closely the European widely distributed form. In our present state of knowledge it therefore appears to be best to mention the more important variations described in the organisms in discussing etiology, but in the clinical account to deal separately only with African tick fever.

HISTORY AND GEOGRAPHICAL DISTRIBUTION

European Variety.—Relapsing fever was prevalent in the United Kingdom in the eighteenth and first half of the nineteenth centuries. In 1868 and 1872 it was prevalent in Berlin, and in 1873 Obermeyer described the spirillum of the disease which he had found in the blood, and which is commonly known by his name, although more correctly termed *Sp. recurrentis*, as it was first so called by Lebert. The disease is endemic in Russia, where the bed-bug was long suspected to carry it, and in 1897 Tictin infected monkeys by injecting the blood obtained from bed-bugs recently fed on a fever patient. More recently relapsing fever has been frequently met with in the Balkan States, Greece and South Russia.

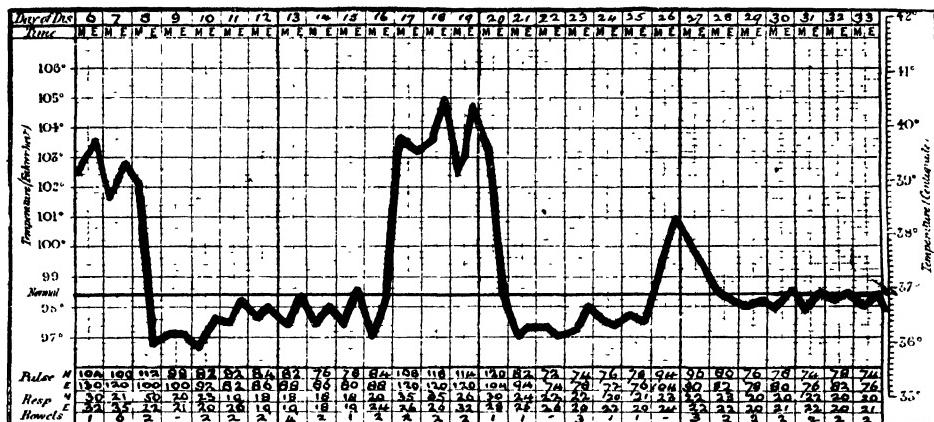
Asiatic Variety—History of Relapsing Fever in the East.—Norman Chevers carefully studied the older records regarding fevers in India, and came to the conclusion that relapsing fever is one of the indigenous pests of the country, and that its history can be traced back until the middle of the eighteenth century. He considered that the outbreak of a fatal fever which followed the drought and famine in the United Provinces in 1816, and again in 1836, was probably relapsing fever. It was not, however, until 1842 that the disease was clearly distinguished from typhus in Europe, and the first Indian outbreak which was recognized as being relapsing fever was that described by Robert Lyall, in the Usufzaie Valley, near Peshawar, in the extreme north-west of the Punjab in 1852–53. The mortality was unusually high, namely, about 30 per cent, jaundice being seen in some, and inflammation and suppuration in the glands occurred in others during the late stages, the people attacked being mainly very poor and half starved. In the 'sixties several outbreaks occurred in the jails of the Punjab and United Provinces, which Dr. O. Boyes Smith showed to be identical with the relapsing fever of Great Britain. Again, the famine of 1876–77 was attended with much relapsing fever in the Bombay Presidency, but not on the Madras side of India, which is in accordance with the present incidence of the disease in its sporadic form. This outbreak was very ably investigated by Vandyke Carter, who first found the spirillum in India, thus identifying the disease with that of Europe; he also reproduced it in monkeys. He wrote a very full account of the disease, which will be further referred to.

The next important contribution on the subject appears to be the account of an outbreak of relapsing fever among the coolies working on the Chaman extension railway in 1890–91 by L. J. Pisani, I.M.S., the death-rate among 91 cases having been 7·8 per cent. In 1899 I met with an outbreak in the Kumaon Hills, which had been reported as Sunjar, a disease previously thought to be a mild form of Mahamari, or plague. On reaching the place the fever had subsided, but full notes of the illnesses of those who had suffered revealed a typical outbreak of relapsing fever, and in the blood of a boy who was just commencing to get his first relapse I found the spirillum in small numbers. The occurrence of the disease in this part of the Himalayas is interesting in connexion with the fact that the 1816 epidemic fever specially affected the districts of the United Provinces just south of the Kumaon. Two cases of fever showing the spirillum in their blood were also seen in Tibet, to the north of the Himalayas, by Turnbull, while the disease has also recently been reported from Peshawar, as well as from the Bombay Presidency, the latter being never long free of it.

Distribution of Relapsing Fever in India.—The exact limits of the distribution of relapsing fever in India are probably not yet fully known, and there is little to be added to the information just given under the head of the history of the disease. There appears good reason for thinking that it does not occur in Bengal, Assam and Madras. In the United Provinces it is certainly very rare, except in the Kumaon Hills, where outbreaks probably are not infrequent; these may possibly occasionally spread to the plains, as appears to have happened in 1816. In the Punjab the disease is probably endemic in the north-western parts, while 3 cases occurred in the Lahore Hospital in 1906, of which Chart 25 is an example; but none in 1904 and 1905. The regular home of relapsing fever,

however, is Bombay, where considerable numbers of cases are admitted to the native hospital every year, and are sent on to an infectious one as soon as their nature is recognized; this is not always easy to do at once. Thus I find that in 1906, 87 cases of relapsing fever were admitted to the medical wards of the J. J. Hospital, five-eighths

CHART 25



Relapsing fever, showing two relapses from a case in Lahore, Punjab.

of which occurred in the first half of the year, and fewest in the wet months of July and August. It is noteworthy that Vandyke Carter found no cases of relapsing fever in the Bombay Hospital records before the epidemic years of 1876-78, so that the endemic prevalence there appears to date from that outbreak.

In China.—Relapsing fever occurs with typhus in the Farther East, where L. Hill found the spirillum in 1905 in Southern China.

Professor L. M. Sandwith has also observed the disease in Egypt.

More recently relapsing fever has been met with in the Darjeeling Hill district by Jukes and by Humphrey with a high mortality and in the Bulandshahr district of the United Provinces by R. Steen and Townsend, by Bisset in Meerut, by Stott in Bangalore in South India, by Browse in Quetta and Smith and Graham in Chitral in North-West India.

In Indo-China outbreaks have been described by several observers since Seguin described it there in 1907, the mortality varying between 8 and 48 per cent.

In the **Philippines** Ashburn, Vedder and Gentry met with it in 1912.

In Persia and Arabia relapsing fever has been described by Dschunkowsky and R. M. Carter respectively, and in both instances was found to resemble African tick fever rather than the Indian form of relapsing fever, as did the Quetta variety with up to seven relapses of Browse.

The American Variety.—This has been seen in New York, in Colombia and by Darling in Panama, where the infection was got from native villages.

ETIOLOGY

The Spirillum of relapsing fever is now classed by most authorities under the protozoa, although differences of opinion still exist on this point. The principal characters of the different varieties are shown in a convenient form in Table XXIII., taken from the paper of F. P. Mackie. He relied largely on the serum reactions for the differentiation of the different species, but Strong, as already mentioned, brought to India a set of white rats immunized respectively against the African, European and American strains of spirochaetae and inoculated them with the blood of Indian relapsing-fever patients containing active spirilla, but found that only the control and the animals immunized against the African disease became infected, proving that the other varieties could not be thus differentiated.

Staining of the spirillum can readily be done by the Romanosky method or one of its modifications; if scanty, stain dehaemoglobinized thick films with gentian violet. In the European and Asiatic forms they are usually numerous in the blood during the fever, disappearing during the apyretic intervals to recur again with the fever. They are much more scanty in African tick fever. The **cultivation of the parasite** is difficult. Duval and Todd in 1908 maintained the virulence of the Sp. duttoni for mice on a complicated egg medium for forty days, while in 1912 Noguchi cultivated all four varieties of blood spirilla by the method employed by him for the Spirochaetae pallidum, and in the following year Hata recorded a success with a more simple medium. Sergent, Foley, Gillot and Beguet have studied the **agglutinating** properties of the spirillum of relapsing fever in Algeria, and found during the first and second attacks no agglutinating power in the patient's blood, but during the apyretic intervals the serum developed both agglutinating and spirillcidal powers, which were not destroyed by heating to 56° C-R^o half an hour. A monkey, which had recovered from a severe attack of relapsing fever, proved immune to further inoculation, showed agglutinating properties in his bl. M^c The property of the blood in recovered cases might be used for diagnostic purposes. In doubtful cases. Noguchi has shown that the Sp. galinarum does not pass through a fine porcelain filter.¹ Rodhain and others found the cerebro-spinal fluid in African tick fever to be free from spirilla or infective properties, and Ardin-Delteil and others have confirmed this observation, and also shown that a definite lymphocyte in this fluid is present during the attacks and apyretic intervals, but disappears on recovery. The removal of the spleen in fowls has been found to increase the organisms in the blood, but to decrease the clinical symptoms.

Animal Infection.—As shown in the table, small rodents, mice and rats, and monkeys are the most susceptible animals, while rabbits and guinea-pigs have also been infected. Dogs, cats, goats and pigeons are refractory.

¹ Todd and Wolbach, however, found that Sp. duttoni could be made to pass through a fine porcelain filter under 50 lb. of pressure to the square inch, and monkeys were infected with the filtrate.

TABLE XXIII.—VARIETIES OF RELAPSING FEVER, AFTER MACKIE

	European. Sp. obermeieri (recurrentis).	Asiatic. Sp. carteri.	American. Sp. novyi.	African. Sp. duttoni.
Minimal length	12	12	7-9	13
Shape	Spiral	Open flexures	Regularly spiral	Open flexures
Flagella	Peritrichous	?	Terminal (Novy). Peritrichous (Fraenkel)	Peritrichous ?
Animals susceptible	Small rodents only after passage through monkeys	Small rodents infected with difficulty	Small rodents very susceptible	Small rodents and many animals very susceptible
Course in animals	Mild	Very mild	Severe	Very severe
Sub-inoculations in animals	Monkey to monkey, and mouse to mouse. Positive (Fulleborn and Meyer)	Monkey to monkey, and mouse to mouse. Positive (Mackie)	Monkey to monkey, and mouse to mouse. Positive	Monkey to monkey positive; same for most animals (Breinl, Kinghorn and Garrett)
Course in man	One, sometimes two relapses	Severe, one or two relapses	?	Severe, four or five relapses
Parasite in human blood	Heavy infection	Variable	?	Very sparse
Natural transmission	?	By lice (?)	?	By ticks
Serum reaction	Immune serum without any effect on novyi and duttoni	Immune serum without effect on novyi	Immune serum without effect on obermeieri, duttoni or carteri	Immune serum without effect on novyi or obermeieri

Transmission.—The relationship of verminous insects to the spread of relapsing fever has long been suspected and more recently proved. Thus as early as 1891 Flugge suggested lice as the carriers of European relapsing fever, while in 1894 Tictin infected monkeys by injecting powdered-up bugs recently fed on a relapsing-fever patient. F. P. Mackie, I.M.S., in 1907 noted a close relationship between the prevalence of body-lice and an outbreak of relapsing fever in India, and found 24 per cent of the lice infected with the spirillum, which chiefly multiplied in the stomach, and also in the secretions expressed from the mouth, the upper intestine and the ovaries. Head-lice were found by him to be free from

blood, although later Stefansky also incriminated this insect. Bisset also found body-lice to convey the disease in India and Vassal in Tonquin. Nicolle, Blaizot and Conseil, working with the Algerian strain of relapsing fever, as a result of very numerous experiments showed that lice fed on infected cases failed to convey the disease by their bites to either man or monkeys. The crushed contents of fed lice contained numerous living spirochaetes, chiefly in the coelomic fluid, which could infect through slight abrasions of the skin or through an intact mucous membrane. Scratching may thus lead to crushing a louse, and infection through the site of its bite from the spirochaetes in its body fluids. They also demonstrated the important fact of the hereditary transmission of infection in the body-louse. They concluded that the disease is not transmitted by the bite of lice, but by the "contaminative" method through minute abrasions in the skin by spirochaetes escaping from the body fluids. Gizemony states that *Sp. recurrentis* can pass through the intact genital mucous membrane.

In the case of the Central African and the American forms of relapsing fever ticks are responsible for conveying the disease. Here again Leishman and Hindle have demonstrated that the infection is carried by means of the contamination of the tick-bite with the infected faeces of this insect. The infection is also transmitted by heredity from the parent to the young ticks, and Leishman has attributed the development in infected ticks of minute chromatin bodies which travel to the ovaries and appear to be responsible for the infection of the young ticks, an observation which was confirmed by Hindle; but further careful investigations by Marchoux and Couvy and by Todd and Wolbach convinced them that Leishman's granules were not a part of the life history of spirochaetes. In Central Africa the *Ornithodoros moubata* and *O. savignyi* have been shown to carry the disease, and probably also other ticks. Todd has found spirilla in the secretions of the coxal and anal fluids of *O. moubata* fed on relapsing-fever blood. Wolbach also noted them in the salivary glands. Neuman found that the rat-louse could transmit *Sp. duttoni*. In the case of the American variety of relapsing fever Darling incriminated the *O. talaje*, and states that Franca in Colombia found the *O. turicata* to carry the infection.

INFECTION AND PROPHYLAXIS

The question of infection is carefully discussed by Vandyke Carter, who brought forward much evidence to show that the disease spreads by contagion. Thus it was introduced into Bombay in 1877 by immigrants from the famine districts, and first spread to those classes of Bombay people who were in closest association with the infected visitors. It spread through families into which it had been introduced for several weeks, attacking the members at a few days' interval. Few of these escape, although their neighbours commonly remain free. In hospital 1 in 4 of the clinical clerks, 1 in 15 of the hospital establishment, and 1 in 25 of the patients of the medical wards, into which relapsing-fever patients were admitted, contracted the disease, but no single case arose in the surgical wards of the same hospitals. In six cases inoculation of the disease at post-mortems occurred, these including two attacks in Vandyke Carter himself with an interval of two and a quarter years between them. The **incubation** period of these last varied from three and a half to seven days, more usually seven days. In Russia inoculations of the

disease produced infection in from five to eight days. The infection is destroyed by drying the blood, and Carter thought it was probably carried by cutaneous transpiration and the breath of the sick, although he did not succeed in demonstrating the spirillum in either. There was no evidence of the spread of the disease by the urine or faeces, and no cases occurred among the hospital washermen. In hospital it did not spread specially to patients in beds contiguous to cases of the disease. V. Carter notes that the disease produced by inoculation precisely resembles that acquired through ordinary channels, both in the time of advent and in general character, but he makes no mention of biting insects as possible carriers of the infection.

Now that it has been shown by Mackie and others that the infection of the Asiatic and European varieties of relapsing fever is transmitted through lice, the prophylaxis of the disease largely resolves itself into the destruction of these vermin, as in the case of typhus fever, under which the requisite methods are discussed (see p. 142).

CLINICAL DESCRIPTION OF RELAPSING FEVER IN INDIA

The classical description of relapsing fever in the East is to be found in Vandyke Carter's book on *Spirillum Fever* published in 1882. It is based on a most minute analysis of some hundreds of cases verified by finding the spirillum in the blood, the most important points of which are included in the following account of the disease.

The Temperature Curve.—By far the most characteristic feature of relapsing fever is the peculiar course of the pyrexia, so that it will be well to commence with this point. The **onset** of the fever is abrupt, usually without any previous indisposition, although slight malaise may be noted for a day or two. The fever begins most usually about sunset, and rarely in the morning (as occurs in so many malarial fevers). The patient begins to complain of chilliness, not amounting to an actual rigor. Severe headache, commonly frontal, pains in the back and limbs, constipation and pain in the epigastrium accompany the commencement of the fever. The temperature rises in a few hours to from 103° to 104.5°, the pulse to about 110 to 120 per minute, and the respirations in proportion, and the pyrexia remains of the high continued type for six or seven days as a rule, although it is only in cases attacked in hospital that the full course is seen. In a series of such cases the duration of the primary, or invasion, attack varied from four to seven days, but in cases admitted later its duration, according to the histories obtained, not infrequently extended to as long as from eight to ten days and rarely slightly longer. Shortly before the critical fall the temperature reaches the acme, or its highest point, during which the symptoms are most severe and the danger greatest. The type of pyrexia is level in over one-third of the cases, frequently it descends, and less commonly it ascends or is convex. A mid descent is rare and a wavy curve quite uncommon. Critical exacerbations occur in not more than 10 per cent.

The Crisis occurs most commonly on the sixth evening or night of the seventh day, often being preceded by a slight increase of the symptoms or by delirium. The main fall of temperature takes place within three or four hours, and is usually complete in six to twelve hours and reaches a subnormal point. It is accompanied by copious sweats,

persistent thirst, and often by symptoms of collapse. The pulse and respirations also decrease markedly, but to a less degree and more slowly than the temperature, while the pulse becomes small and weak from cardiac exhaustion and the surface cold. The slowing of the pulse is very great, the rate falling from 120 or more to 70 or 50 after the crisis. Should the decline in the heart-rate not correspond with the crisis either rapid death, some complication or an immediate rebound of the temperature may be expected. The pains disappear, and the tongue cleans in a day or two, but copious pale urine is secreted. Patients are often brought to hospital in this collapsed state, which may somewhat resemble at first sight that of cholera.

The First Apyretic Interval lasts on an average for eight days, and varies from three to twelve days. During this period there is debility, but the temperature soon rises to normal from the subnormal position at the end of the crisis, while the pulse and respiration gradually slow down to the normal rate. The tenderness of the liver, spleen and abdomen also soon subside. In one case in every six a sudden temporary rise of temperature, or rebound, occurs immediately after the crisis, without any spirilla in the blood; or a secondary fever, due to some complication, such as pneumonia, may be seen.

A Second Attack, or First Relapse, or Recurrence, occurs in half the cases about the seventh day of apyrexia, and closely resembles the first in its general character, but the fever may reach even a higher level, although usually it is of shorter duration. The temperature rises rapidly, sometimes with chilliness, although this symptom is not seen until after the beginning of the rise. The type of the fever is continued in 26 per cent, remittent in 70 per cent, and intermittent in the remaining 4 per cent. The daily range of temperature is greater than in the first attack, but rarely exceeds 2° F. The duration of the pyrexia averages 4·53 days, and varies from one to seven days. The crisis is again abrupt, occurring usually at night or in the early morning, the temperature falling rapidly to subnormal. During the second attack of fever pains and abdominal symptoms are present, as in the first, but there is less enlargement of the liver and spleen. Sickness and also jaundice occur late in the attack in one-third of the cases.

A Second Relapse may follow after another apyrexial period averaging ten days, and being thus longer than the first one. The duration of the fever in these third attacks is shorter than in the earlier periods, being from two to four or five days, not uncommonly commencing with chills. The liver is normal, but the spleen is enlarged and tender in half the cases. The type of the fever is much less regular than in the earlier attacks, not being of the continued type, while intermittent fever is nearly twice as common as the remittent form, and constitutes about half the attacks. In another quarter of the cases only an isolated paroxysm occurred. The crisis in such modified relapses is seldom marked.

Third Relapses still more rarely occur, and only after a prolonged interval of from fourteen to seventeen days, the duration of the fever being from one to three or four days. The fever occurs usually as an isolated paroxysm, the temperature rising abruptly, but remitting more gradually.

A Fourth Relapse was seen in 1 case only after a further interval of eleven days as a distinct isolated paroxysm of two days' duration.

In 98 out of 441 cases, or 23·8 per cent, no relapse took place, the fever being of the abortive type with one attack of pyrexia only. In 42 cases contracted in hospital, or inoculated, 21·4 per cent were abortive. In about 20 per cent second relapses occurred, in 5 per cent third ones, and in 2 per cent only did a fourth relapse appear. Chowsky met with one relapse in 50 per cent, a second in 7 per cent and a third in 3 per cent.

Special Symptoms.—Headache is an early and prominent symptom during the fever in 70 per cent of first attacks, but less marked during relapses. It is usually frontal or extending to the temples, and rarely general or occipital only. It may recur without fever about the date of an expected relapse, or persist with lysis in bad cases.

Pains in the Muscles, Joints and Bones are probably always present, and were complained of during the pyrexia in over 70 per cent of cases, mostly in relapses. They were of a gnawing, aching or even intense character, and were also met with in the nape of the neck and the loins. There was no local swelling, but the joint pains were especially persistent.

Sweats are common during remissions of the pyrexia, and especially at the crisis, when in nine-tenths of the cases they may be very excessive. The sweat is acid in reaction, but free from spirilla. Sudamina may accompany the sweats, appearing most commonly at the root of the neck, or front of the body. **Thirst** is invariable during the fever, and may persist after the crisis.

Vomiting occurred in 75 per cent of cases seen in the early stages, but was noted in only 10 to 12 per cent of those admitted late in the first attack and in 20 per cent of relapses. Usually it is not urgent, but may contain specks or streaks of blood, though black vomit is quite rare, being only seen in 2 per cent. Bile, however, may be much more frequent and is sometimes profuse.

The Tongue is generally dry with brown fur on the dorsum and red edges, with sometimes a strawberry appearance. It becomes moist with the fall of temperature and then soon clears. In the early stages it may be clean and moist with a high temperature—a combination which Chowsky regards as pathognomonic of relapsing fever.

The Bowels are constipated in one-third of the cases at the invasion, and in 70 per cent at the acme. Diarrhoea is rare until the close of a febrile attack, when a post-critical flux may occur, especially in severe and fatal cases. Blood in the stools and gurgling in the right iliac fossa are rare, but dysentery may supervene as a complication in natives. Malaena only occurred in 2 per cent.

Epigastric Tenderness and Distension were present in at least 20 per cent of first attacks, and in 30 per cent of relapses of varying degree, and were often associated with muscular rigidity.

The Liver showed some enlargement during the fever in 33 per cent of surviving and in 50 per cent of fatal cases, and in the apyretic intervals in 10 per cent. Pain and

great tenderness were also often present, but in only one case was any inflammation of the serous coat found post mortem.

The Spleen was enlarged in nearly half the total cases, and in 75 per cent of the fatal ones and 40 per cent of survivors. It progressively enlarges during the pyrexial attacks, so is more frequently increased in size during the relapses than in the primary attack. During the non-febrile intervals it decreases to nearly the normal size, while pain over the organ disappears with the crisis. At the acme of the disease the spleen is enlarged in 90 per cent of cases. Post-mortem enlargement (one case weighing as much as 36 oz.) infarcts, softening, and very rarely inflammation were found.

Circulatory System shows little change beyond the rapid soft pulse without any dicrotism. Epistaxis only occurred in 5 per cent, usually at the acme of the first attack. The right side of the heart may sometimes be found to be distended post mortem, and there may also be found small petechial haemorrhages especially on the parietal pericardium, while the first sound is often weak at the crisis. Thrombosis of the femoral vein was met with once only. Spontaneous gangrene occurs.

Respiratory System.—In fatal cases, congestion of the lungs and pneumonia are common. In half the cases, cough with slight bronchial congestion, frothy expectoration, and in 54 per cent of invasion attacks, coarse moist sounds are present, which may pass on to bronchitis and pneumonia, the former being rare without the latter.

The Urine contains a trace of albumen during the pyrexia in 1 case in 6, especially at the acme of the first attack : but no evidence of organic disease of the kidneys was met with. It is generally scanty and high-coloured, and frequently contains bile pigment. Haematuria also occurs in 3 to 5 per cent.

Jaundice was noted in 15 per cent of surviving cases, most frequently during an invasion attack, but also in 56 per cent of fatal ones, in whom it is often very marked.

Rash.—Vandyke Carter describes and figures an eruption which occurred in 10 per cent of the cases. It is rare before the fourth day, and commonest at the acme of either the first attack or a relapse, and may persist during the apyrexial interval. It appears on the front and sides of the chest or abdomen, or on the arms, but more rarely on the legs, as clusters of minute red blotches or stains from the size of a pin's head to a pea, hardly raised, flattened, circular or irregular with well-defined edges, and not effaced by pressure. These sometimes fade rapidly, but more often become dark purple and last several days, while they may also become petechial. They are usually few in number, from six to twenty-four or more, and were not seen in infants. They rather resemble those of typhus in appearance, and of typhoid in their grouping, but they have also been observed in remittent fevers and pneumonia, and therefore are not pathognomonic of relapsing fever.

Less Common Complications.—Cerebral haemorrhage was found in one-sixth of the autopsies. It affected the pia-arachnoid membranes, mainly on the vertex, from 2 to 8 oz. of blood being effused. Meningeal symptoms have also several times been

described. The meningitis produced unconsciousness about the end of the fever, and was always fatal. The conjunctivae may also show ecchymoses. Inflammation of the eye, especially iritis, occurred in 1 per cent of cases in Bombay, and in debilitated subjects may lead to destruction of the organ. Herpes labialis is not very infrequent. Abortion with profuse haemorrhage may be fatal in females. Parotid inflammation or suppuration occurred in 2 to 3 per cent. When double it is usually fatal, but if single it resolves without suppuration in half the cases, the other half require incision. This complication may cause the fever to be mistaken for plague. Congestion and minute petechiae occur in the stomach, while fatal haematemesis was twice seen, but was not accompanied by jaundice, as is the case in yellow fever. Congestion, inflammation and petechiae are also found not infrequently in the intestines post mortem, especially when diarrhoea has been present during life. These changes are most marked in the ileum, but no ulceration was ever found, while the Peyer's patches very seldom showed any congestion, and the mesenteric glands were always healthy, so that the lesions never resemble those of typhoid fever.

CLINICAL MODIFICATIONS OF RELAPSING FEVER

Cases of this fever, in which both the crisis of the invasion attack and one or more relapses are seen, can hardly be confused with any other disease, and are readily recognizable clinically. In practice, however, the patients often only come under observation after the first crisis, when in a more or less collapsed condition, while the spirillum is absent from the blood, and the case may not become clear until the parasite reappears with the recurrence of pyrexia after about seven days' interval. Such cases are frequently seen in the Bombay hospitals at the present day, and often cannot be diagnosed until the relapse occurs. More difficult still may be the numerous cases admitted late in the invasion attack who do not suffer from any relapse, although the crisis is frequently sufficiently characteristic to be of diagnostic value.

In addition to the above difficulties in typical cases, still greater ones arise where the disease runs an atypical course. In the first place, it is by no means very rare for the primary and sole attack to be short and somewhat irregular, so much so that at least one-fourth of Vandyke Carter's cases were of obscure, irregular or anomalous character, and were recognized only by the presence of spirilla in the blood, by which test alone many aberrant forms were detected. The variations from the typical course may be in two different directions. In the first place the fever may be of a short, irregular remittent type, instead of a continued type, and thus closely simulate a malarial fever, and such cases can only be detected by finding the spirillum in the blood.

A second, and still more important, variation is a prolongation of the pyrexia so as to cause the disease to resemble very closely typhus fever. These cases were described by Carter under the term **Icteric Fever**, or bilious remittent fever. They constitute an unusually fatal form of relapsing or spirillum fever, distinguished by deep jaundice, generally accompanied by an eruption of red spots or petechiae, and irregular prolonged pyrexia, early prostration and a tendency to localized inflammations. They form about 5 per cent of admissions, and 15 to 20 per cent of the fatal cases. The pyrexia is typical in

the invasion, although somewhat below the mean throughout, and often persisting for seven or eight days, and tending to fall by lysis in the worst cases. Intense jaundice is invariable and appears early with great depression, while a typhoid-like state was very common. The death-rate was 70 per cent, and in 14 out of 20 cases the spirillum was found, while there were reasons for regarding the others as true relapsing fever simulating typhus, the latter being unknown in Bombay. These cases were also mistaken for yellow fever, which is absent from the East, while black vomit was never present in these jaundiced cases according to V. Carter, but Chowsky mentions the occurrence of various forms of haemorrhages, including haematemesis, malaena, haematuria, and epistaxis, the last in 10 to 15 per cent of his cases, generally just before the crisis. These may recur with a relapse. The jaundice appears to be toxæmic in nature producing haemolysis, iron having been found by Mackie in great excess in the liver and spleen.

An outbreak of relapsing fever, with some similar typhus-like cases, has recently been described by W. T. McCowen, I.M.S., at Surur in the Bombay Presidency, and similar cases appear to have been present in the Chaman Railway outbreak already mentioned, so their occurrence should always be borne in mind, and the spirillum sought for in the blood.

The Mortality of relapsing fever in 616 cases of Vandyke Carter where the spirillum was found in the blood was 18·02 per cent, and among 69 contagion cases in hospital it was 26·1 per cent. These figures are much higher than those met with in European outbreaks, which were 4 per cent in British hospitals, 4·3 to 7·2 in Breslau, and 14·97 at St. Petersburg in 1865. The difference is partly, but not altogether, due to the famine condition of many of the patients. A little over half the deaths occurred at the acme of the first attack, about one-fourth in the first interval, one-fifteenth in the first relapse, and the rest later, often with complications such as pneumonia, cerebral haemorrhage or exhaustion. During recent outbreaks in Bombay, Chowsky had a mortality of 30·7 per cent, which rose as high as 39 per cent in 1902 with famine and overcrowding. Among 300 converts, however, who were under good sanitary conditions, it was only 5 per cent, or about the same as in Europe. The rate was the same in men as in women, but only half as great in children. In the Bulandshahr district of the United Provinces, Steen recorded a mortality of 26·5 per cent; in Indo-China, Seguin had a death-rate of 8 per cent, and Vassal in Tonquin one of 48 per cent; so that the death-rate evidently varies considerably in different outbreaks.

Prolonged irregular first attacks ending by lysis, and marked jaundice, as in the bilious form, are of bad prognostic import.

THE BLOOD CHANGES IN RELAPSING FEVER

The number of red corpuscles and the percentage of haemoglobin are said to be somewhat reduced during each febrile period. More marked are the changes in the white corpuscles, leucocytosis of the polynuclear type being associated with the fever paroxysms, reaching its height about the time of the crisis but persisting for a day or two only after it. Phagocytosis of the spirilla also occurs. This increase of the leucocytes is an important

help in differentiating the fever from typhoid, malaria, and other fevers unaccompanied by an increase in the white corpuscles.

The Spirillum obermeieri is, however, the most important feature of the blood changes, for it is present throughout the febrile paroxysms in increasing numbers, but disappears rapidly from the peripheral blood at the time of the crisis, and is absent during the apyrexial interval. The organisms can be readily seen in fresh unstained blood as spiral thread-like bodies with active movement, often radiating from a common centre. They stain easily with fuchsin, or Romanosky's stain, including its many modifications; they are best seen with an immersion lens on account of their extreme thinness.

Lowenthal's Reaction.—The difficulty in diagnosing relapsing fever microscopically during the intervals with no spirilla in the blood can be got over by Lowenthal's ingenious method. A drop of blood from the suspected cases is mixed with another drop containing spirilla from a case in the febrile stage, sealed under a cover-glass, and incubated at blood-heat at least for half an hour. If the case is not relapsing fever the majority of the organisms will still be motile, but if they have become quite motionless and clumped in regular masses, a control specimen giving a negative result not more than two and a half hours after, relapsing fever can be safely diagnosed.

Diagnosis.—A typical relapsing fever is easily distinguished from any form of malarial fever by its sustained high temperature without the remissions and intermissions of the latter disease. During relapses, especially the later ones, a markedly remittent or intermittent curve may be seen, which can only be surely differentiated by a microscopical examination of the blood. Similarly the typhus-like cases can often only be diagnosed by finding the spirillum. The disease can rarely be mistaken for typhoid on account of the much longer pyrexia terminating by a slow lysis of the latter disease, which also usually shows general abdominal distension and iliac tenderness instead of the epigastric distress of relapsing fever. Yellow fever is only superficially simulated by the bilious form of relapsing fever; black vomit is absent in the latter disease. The more continued type of seven-day fever might for a time possibly be mistaken for relapsing fever during an outbreak of the latter disease, but the symptoms are less severe, while the slow pulse of this disease is never seen during high temperature in relapsing fever, which, moreover, is as rare in Europeans in India as seven-day fever is common among them.

Treatment.—The introduction of salvarsan and neo-salvarsan has completely revolutionized the treatment of this disease, as they have a definitely specific action on the causative spirochaetes, as shown in Ehrlich and Hata's monograph in 1911, and repeatedly confirmed by subsequent writers. The drugs are best given intravenously in comparatively small doses, different writers recommending from 0·15 up to 0·3 or 0·4 gm. of salvarsan. Rodhain states that 0·01 gm. per kilo is completely curative, but smaller doses may be followed by relapses. Given by the rectum salvarsan proved useless. Galy gives equally good results, and is thought by some to be less depressing than salvarsan itself. Other arsenical preparations, such as atoxyl, arrhenal, cacodylates and hectine, are very inferior to salvarsan.

In the absence of salvarsan and its modifications in Servia F. Hagler found quinine

in 10-grain doses with Liquor arsenicalis min. $7\frac{1}{2}$ three times a day, or even larger doses, shortened the fever and lessened the frequency of relapses. Tartar emetic has been tried without much success by Conseil. Organic mercury preparations have also failed experimentally in animals. A 1 in 1000 solution of adrenalin chloride in 5- to 30-minim doses has been recommended for heart failure.

Another variety of relapsing fever produced by a spirillum infection has been known in Africa since the days of Livingstone as tick fever, although the spirochaeta was only found in 1904 by P. H. Ross and A. D. Milne in Uganda. Dutton and Todd studied the disease on the Congo, and succeeded in conveying the infection by the bites of a tick (*Ornithodoros moubata*) previously fed on the blood of a patient infected with the disease. They also proved that the disease can be transmitted by the larvae hatched from the eggs of an infected tick. A warm temperature appears to be required for the development within the tick, which accounts for the absence of infection on the higher parts of central East Africa. The organisms are very scantily present in the blood, and thus often require long search of stained specimens with an oil immersion lens for their demonstration. Polynuclear leucocytosis is well marked. Romanosky's method and its modifications stain the organisms well. If the organisms are scanty a small thick smear after drying is dehaemoglobinized by placing in water without fixing, and then stained with gentian violet for five to ten minutes, or by Leishman stain. When the spirochaetes cannot be found in the blood microscopically the disease may still be produced in monkeys by injecting them with the patient's blood, and after some days abundant organisms will be present in their blood; but this method of diagnosis takes some time.

In Europeans the disease is a severe one, beginning with a rapid rise of temperature to 104° or 105° F., with intense headache and vomiting, which may become bilious. The pyrexia lasts for from one to three days and ends by crisis, falling to below normal with disappearance of the symptoms. After an interval, which may vary from one day to three weeks, but usually from six to ten days, a relapse occurs of nearly equal severity with the initial attack. Relapses are usually repeated five or six times, or sometimes considerably oftener, but with increasingly long apyrexial intervals. Death is very rare, but great weakness remains for some time. In natives the disease runs a much milder course, and relapses are rare, a considerable degree of immunity having been produced by repeated attacks. In monkeys the disease runs a long course with relapses, in which respect it differs from Indian relapsing fever. The use of the microscope is necessary to differentiate this fever from malaria. Among the points of difference from malaria Moffat mentions the absence of rigors in relapsing fever, and the presence of enlargement and tenderness of the liver, while the tongue is covered with thick white fur, the respirations are quick and there is pain in the chest.

The most important **complication** is iritis or irido-cyclitis, which is common in relapsing fever, but very rare in malaria. Severe epistaxis also occurs, and may even be fatal in debilitated subjects. Pneumonic complications are serious, while fatal syncope is liable to occur. Unilateral facial paralysis is also not uncommon.

The Treatment is the same as that already described for other forms of relapsing fever, salvarsan being the most effective drug, but expensive. When cases are numerous

the following combination is recommended by De Buddere as less costly and easily administered : Atoxyl, 10 gm., Sublimate, 0·3 gm., Potassium Iodide, 2·5 gm., Distilled water, 100 gm. From 3 to 4 c.c. to be injected intramuscularly twice a week. Great improvement in the temperature and relief of headache and photophobia result, but relapses are not always prevented by this treatment. Digitalis and strophanthin and absolute rest are necessary to prevent heart failure.

The Prophylaxis consists in avoiding sleeping in native huts or on infected sites, which are almost invariably infested with ticks containing the spirochaete. Thus Kleine and Echard found that 23 out of 45 ticks collected in East African native huts were able to infect monkeys, while spirochaetes were demonstrated in 18 of them as well as in the eggs of most of them. Moreover, Moellers starting with 110 ticks was able to infect a series of monkeys over a period of one and a half years, in the course of which the spirochaetes were transmitted through several generations of the insects. The infection may thus cling to huts for a long time. A well-tucked-in mosquito-net is some protection against ticks.

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VI. INFECTIVE JAUNDICE OR SPIROCHAETOSIS ICTEROHAEMORRHAGICA

History.—Epidemics of jaundice have been described from the earliest times, and have been particularly frequent in armies during war. More recently a number of French writers have described epidemics accompanied by jaundice, especially Landouzy in 1882 and Mathieu in 1886, while subsequently Weil described 4 cases, and the disease has often been called after him without sufficient justification. It was not, however, until the Japanese worker Inada and his assistants in 1914 discovered the causative spirochaete that the disease has been clearly distinguished from catarrhal and other forms of jaundice and its etiology placed on a firm basis. Their work has been confirmed by Bertrand Dawson and Hume and by Stokes and Ryle as a result of the study of cases in the armies in France and Belgium and by Martin and Pettit and other French investigators.

Geographical Distribution.—The discovery of the causative organism of the disease has been too recently made to allow its distribution to be worked out, but cases have already been verified in Japan, Flanders, France, Italy and the Eastern front, while infective jaundice has long been known to be wide-spread over the world, including India.

ETIOLOGY

The first description in the English language of the discovery of Inada and his colleagues appeared in 1916, although the organism was found in 1914 through the inoculation of the blood of a patient into a guinea-pig, in whose liver numerous spirochaetes were subsequently found after the animal had died with symptoms resembling those of the human disease. The Spirochaeta icterohaemorrhagica is most commonly 6μ to 9μ in length, but may vary between 4μ and 13μ or even more. The thickness is about 0.25μ , and shows two or three large and four or five smaller waves in the body. Under dark ground illumination it presents a granular appearance, while its motility is slow and undulating with side-to-side movement of one or both ends on the centre, and it is much less refractile than *Sp. pallida*. It may be stained with Giemsa in two to thirty-six hours, Leishman in thirty minutes, or better still by the method of Fontana, which consists of staining with an ammoniated silver nitrate solution after first fixing with 5 per cent aqueous solution of tannic acid. In sections of organs and tissues the Levaditi process is best. The organism has been cultivated by the Ito and Matsuzaki in a semi-solid blood

agar or blood gelatine with a layer of paraffin added to the surface of the tubes, best at 20° to 25° C., and in fluid media containing ascitic, or better pleural, exudate. A clear culture medium may be made of one part of horse serum with four parts of agar solution containing 15 to 30 per cent gelatine.

Animal Infection is most readily obtained by injecting about 3 c.c. of the blood of a patient or infected animal into the peritoneal cavity of a guinea-pig, which develops fever and jaundice after 6 to 8 or more days, but the incubation period becomes shortened to 4 days after repeated passage with increase in virulence. The animals die in 5 to 10 days, and the liver shows the most numerous infection, several spirochaetes being found in an oil immersion field of a stained smear of this organ. The blood of infected patients is nearly always infective during the first five days of the disease and less certainly up to the tenth day, after which results are usually negative. More recently field rats have been found to be infected in Japan, in Flanders and in Brazil, guinea-pigs having been infected from them. In the severe Japanese form of the disease the spirochaetes are frequently found in the urine, from which guinea-pigs can be infected, but in the milder Flanders form Stokes and Ryle failed to find them in the urine of their patient.

Possible Modes of Infection.—Guinea-pigs can be infected orally or by applying infective material to the shaved skin, and the Japan workers think infection of man may commonly take place through the skin, as their cases mainly occurred in very wet mines, while the urine of their patients contained the organism. Recently the proof that rats are infected throws fresh light on the problem, which requires further investigation. Stokes experimented with lice with negative results, while he found the infection to be closely associated with work in certain very wet trenches in Flanders.

Prophylaxis.—Little can be said on this head owing to the deficiencies of our knowledge of the modes of infection. In Japanese coal-mines the disease has been much reduced by pumping operations rendering them drier. In Flanders the provision of long water-tight boots for use in wet trenches also appears to have had a good effect in lessening the number of cases.

CLINICAL DESCRIPTION

Clinically the disease is an extremely variable one, ranging from typical severe cases with high fever, deep jaundice and extensive haemorrhages often ending fatally, to very mild febrile conditions without jaundice or other very distinctive signs. Nevertheless the blood of these mild cases produces infection of guinea-pigs when injected into them. The following brief account is mainly based on the publications of English workers in France and Flanders, where the disease is milder than in Japan, typical cases being first described.

The Onset is quite sudden, often with a shivering fit or faintness, followed by a high rise of temperature, sickness, pains in the head, back and limbs, and prostration. Pains in the eyes and in the upper part of the abdomen also occur.

The Fever shows a sudden initial rise to from 103° to 105° F., and runs an irregular course between 100° and 103° for about a week, and then tends to fall by lysis to terminate about the tenth to the fourteenth day, and may become subnormal for three or four days. In some cases there is then a secondary rise of temperature about the beginning of the third week lasting for ten to fifteen days without usually any exacerbations of the symptoms. In mild cases the duration of the fever may be much shorter and less characteristic and be indistinguishable clinically from "trench fever."

Jaundice is the most characteristic feature and appears about the fourth day and deepens up to about the eighth to the tenth day, and then usually fades rapidly. The skin is usually of from a lemon yellow to a deep orange tint, and rarely reaches the green hue of complete obstructive jaundice. Convalescence begins about the end of the fourth week, and the disease does not leave any untoward symptoms behind it.

The Alimentary System shows the following changes. The **tongue** is dry and brown and may become fissured. **Herpes labialis** of an haemorrhagic type occurred in 42 per cent of Stokes' cases. Sickness is nearly a constant symptom in the early stages and may persist for several days and become bilious. Hiccup may occur in severe or fatal cases. The **bowels** are nearly always constipated, but both diarrhoea and malaena may occur in bad cases. The stools are usually slightly bile-stained, showing that the obstruction of the bile-duets is not complete. The **liver** is frequently enlarged and may extend three fingers'-breadth below the ribs and be very tender. The **spleen** is rarely palpable.

The Pulse is slow in proportion to the temperature even in the absence of jaundice, and may be only 100 a minute with a temperature of from 104° to 105° F., but the tension is usually good and the blood pressure is not reduced as it is in typhoids.

The Lungs usually show signs of bronchitis; or haemoptosis may occur, but pneumonia is not found.

The Nervous System reveals the effects of the disease in weakness and prostration in addition to the pains already mentioned, while in fatal cases coma may be a terminal symptom. The conjunctiva is jaundiced, and in the early stage congested. Meningitic complication was frequently noted by Costa and Troisier, namely, in as many as 90 per cent, stiffness of the neck and Kernig's sign being present. The cerebro-spinal fluid was under pressure and contained febrin and polynuclear leucocytes, and guinea-pigs were infected with the fluid, showing the presence of spirochaetes in it.

Haemorrhages are very characteristic of severe cases, and occur in the forms of epistaxis, haemoptosis, haematemesis and malaena, and purpuric eruptions on the skin, while profuse urticaria has been recorded.

The Urine, in addition to containing bile, also almost constantly shows albumen varying from a trace up to one-sixth part on boiling and standing. Acetone is also found in grave cases. Leucin and tyrosin were not found to be present by Stokes and Ryle.

Both hyaline and granular casts are readily found, and red corpuscles may also be present. The spirochaete may sometimes be found by centrifuging and appropriate staining.

The Blood shows a slight degree of anaemia in severe cases, and a polynuclear type of leucocytosis, amounting in some cases to 25,000 white corpuscles according to Japanese workers and Dawson and Hume, although Stokes and Ryle found in the early stages only from 9000 to 10,000. The last-mentioned workers found the resistance of the red cells to haemolysis rather higher than normal. The spirochaete is very difficult to find in the blood in human cases.

The Mortality in Japan was from 20 to 30 per cent, but in Flanders Stokes and Ryle found it to be under 6 per cent, and Dawson and Hume and Bedson give it as 4 to 5 per cent, while in Italy among 361 cases it was only 0·55 per cent according to Moreschi.

The Incubation according to Inada is seven to eight days, while in a laboratory-infected case Stokes found it to be from the sixth to the eighth day.

A Mild Form of the disease without jaundice has been shown to occur by Stokes, who produced the disease in guinea-pigs by injecting them with the blood of such cases. Indeed in no less than 26 per cent of his cases this sign was absent. Even fever, it is said, may be absent, and in very mild cases the disease can only be certainly recognized by the guinea-pig test.

The Diagnosis is not usually difficult in typical jaundiced cases, especially if haemorrhages are also present. In the Dardanelles in 1915 jaundice was frequently met with together with paratyphoid fever, but according to C. J. Martin this was due to the coincidence of unusual prevalence of the two diseases, and jaundice is very rare in uncomplicated paratyphoid. Unfortunately the Dardanelles outbreak occurred before Inada's work was known, so spirochaetes were not sought for. In the early stages before the appearance of jaundice, and in the mild type not showing that sign, the diagnosis may be very difficult, especially from "trench fever"; but as a number of cases commonly occur at about the same time the typical ones will lead to suspicion in the case of the mild ones, and the guinea-pig test may confirm the suspicion, although this will take from eight to ten days to carry out. In the exceptional cases in which the spirochaete can be found in the peripheral blood the diagnosis can be made more quickly. Dawson and Hume have used Marris's atropine test for diagnostic purposes. This test depends on the fact that in typhoid and the paratyphoids an injection of one-thirtieth of a grain will produce an increase of only ten points or less in the pulse rate within one hour when it is slow. In infective jaundice and other conditions the usual release of the pulse takes place.

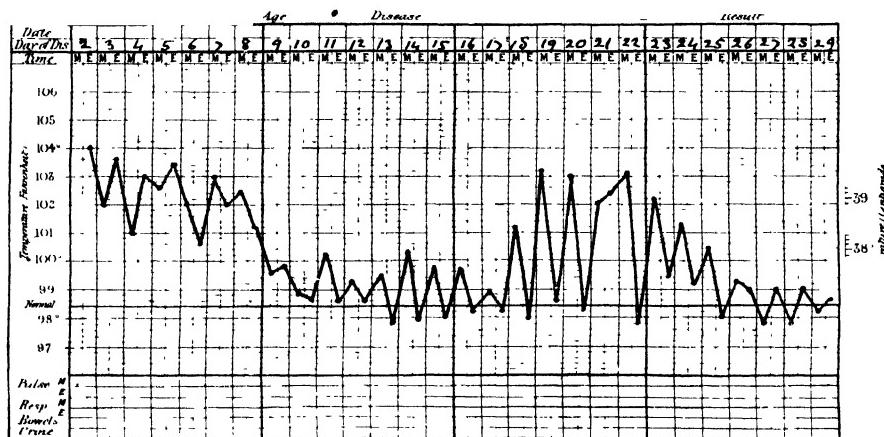
The Morbid Anatomy has been carefully studied in fatal cases, which show deep jaundice of the tissues, haemorrhages in the pleura and lungs, peritoneum, kidney, heart, muscle and endocardium, kidneys and suprarenals. The duodenum is often congested and the termination of the common bile-duct obstructed, although according to Dawson and Hume the common bile-duct itself is healthy. The liver shows little naked-eye change, but microscopically there is bile stasis and leucocyte infiltration, but little cellular

degeneration. Stokes found the kidneys to show swelling and granular degeneration of the tubular epithelium, exudation of polynuclear leucocytes and haemorrhages into the tubules.

Treatment.—This is mainly symptomatic with good nursing. Fluids should be given freely during the fever, including alkaline draughts. Saline purges or enemata may be required for constipation. For vomiting and acetonuria Stokes advises rectal administration of one pint of 6 per cent solution of glucose once or twice daily, and he gives fruit to eat.

Inada and his colleagues have shown that during convalescence the blood of patients contains immune bodies which suffice to protect guinea-pigs against infection, and they have recently used a serum prepared from horses by inoculating them with cultures, a treatment which apparently promises results. They also tried a vaccine for protective purposes without much success. The serum treatment is worthy of further study, and may very possibly prove of great value in severe cases.

CHART 26



Infective Jaundice (Bertrand Dawson).

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VII. UNDULANT OR MALTA FEVER

Synonyms.—Malta fever, Mediterranean fever, Rock or Gibraltar fever, and Undulant fever, the last being a convenient term suggested by Hughes to avoid the errors incidental to the former geographical names. Malta fever, however, is the name in most general use, while nearly all our knowledge of the disease has been obtained through researches carried out in that island, mainly by the Officers of the Royal Army Medical Corps.

History of the Differentiation of Malta Fever.—Louis Hughes, R.A.M.C., in his work on Undulant, Malta or Mediterranean fever, gives a full account and bibliography of the earlier writings on the subject. It will suffice here to mention that he came to the conclusion that the disease has been endemic in Malta and Gibraltar at least since the beginning of the nineteenth century, and probably for much longer, but that it was not recognized as a distinct type of fever until 1859, when Marston took up the question. He published an exhaustive description of it under the name of "Mediterranean remittent or gastric remittent fever" with post-mortem reports, and clearly distinguished between it and typhoid fever, in a paper in the *Army Medical Blue-book* of 1863. Another very important contribution is that of Surgeon-Major Veale in the Army Medical Report, published in 1881, in which he describes cases of Malta fever seen at Netley and draws a clear distinction between it and malarial fever.

It was not, however, until by his classical researches Colonel, now Major-General Sir David Bruce, of the Royal Army Medical Corps, discovered the *Micrococcus melitensis* in the spleens of Malta-fever cases in 1886, isolated it in pure culture and reproduced the disease in monkeys, from which he again recovered the organism, that the specific nature of Malta fever was firmly established. Hughes soon after confirmed this important discovery, and wrote an excellent monograph on the disease.

History of Malta or Undulant Fever in the East.—The discovery of the serum test for typhoid and its extension by Sir A. E. Wright to the diagnosis of Malta fever enabled him, with F. Smith and D. Semple, R.A.M.C., to demonstrate the occurrence of Malta fever in India and Hongkong by obtaining reactions in high dilutions of from 1 in 150 to 1 in 1000 in soldiers invalided to Netley from those countries. The patients from India all came from the Punjab, *and some of them had never served in Mediterranean stations*. In 1899 Birt and Lamb carefully studied the serum test for Malta fever at Netley by means of Wright's macroscopical test with dead sterilized cultures (see p. 180). They obtained only incomplete reactions up to 1 in 10 in controls, but never complete ones even

at that dilution. On the other hand, in Malta-fever cases the average dilution giving a complete reaction was between 1 in 600 and 1 in 700. Among 44 cases tested in high dilutions 72 per cent gave complete reactions in dilutions of from 1 in 100 to 1 in 1000 or over, while in only 6 per cent were reactions of less than 1 in 50 obtained. In monkeys infected with the disease Wright and Semple obtained serum reactions as early as the fifth day. In 1900 Lamb obtained complete reactions by the same method up to 1 in 100 in 4 fever cases in Bombay and to 1 in 20 in a fifth, and in the following year E. W. Greig, I.M.S., obtained similar results in 3 cases in the Swat Valley (Punjab frontier).

During the next few years very numerous cases in the Punjab and Bombay were diagnosed as Malta fever on the strength of serum reaction in dilutions of only 1 in 10 to 1 in 40, and even kala-azar was declared to be an epidemic Malta fever on the same grounds, but inquiry showed that the cultures in use were unreliable, and much doubt was thrown on the view that Malta fever is common in India. In 1905, however, Lamb and Pai isolated the *Micrococcus melitensis* from the spleens of 11 cases, which agglutinated in high dilution with a known Malta-fever serum and produced the disease in monkeys, thus finally establishing the presence of the disease in India. Most of these cases occurred in the Punjab, where W. C. H. Foster also met with cases and found the infection in goats. C. N. C. Wimberley has reported the disease from six Punjab cantonments, so undulant fever is widespread in North-Western India, especially in places occupied by British troops.

Distribution of Malta or Undulant Fever.--The synonym Mediterranean fever best indicates the distribution of the disease in Europe, as every country bordering on this sea has been found to be infected with the disease, as well as most of the numerous islands it contains. Nor is it limited to the coastal areas, but has been found far inland in Italy, France, Spain and Portugal. In Africa cases have been reported from the Sudan by Bousfield and Uganda by Bruce, while in South Africa the disease has been found to be widespread by Birt, Strachan and Garrow, and German South-West Africa and North Nigeria are also infected.

In India the disease is not uncommon in British troops in Punjab cantonments, but in the records of the Civil Medical College Hospital in Lahore I found only 4 cases in three years. The disease is rarer in the United Provinces than in the Punjab, while in Bengal I only know of its very occasional occurrence in sailors from the Mediterranean, and it appears to be equally rare in Madras, although occasionally seen in Bombay.

In the **Farther East** Craig reported it from the Philippines, while China is also infected.

In America the old endemic area has been found in Texas in the Southern States, which extends into Mexico, and it has also been reported by Barton in Peru.

In every infected country goats' milk is used for human consumption, and the intimate relationship of the disease to the use of milk from infected goats, which was first established by Bruce's Malta Commission, has been confirmed on all sides.



The Bacillus Pestis of Plague

PLATE III.

The Micrococcus Melitensis of Malta Fever.

MODE OF INFECTION AND PROPHYLAXIS

Until very recently nothing definite was known as to the mode of infection of Malta fever, and consequently prophylactic measures have been largely futile. Hughes brought forward much evidence to connect the disease with bad sanitation, but in Malta, and still more farther east, such conditions are so nearly universal that it is very difficult to prove or disprove their causal connexion with any particular disease, and the work of ameliorating such insanitary states is always a slow one. No further advance was made regarding the infection of Malta fever until the appointment of the Commission of the Royal Society in 1904 to investigate the subject systematically in Malta, but during the three short years that this work has been going on results of much practical importance have been obtained. They have been so well summarized by Colonel David Bruce that a brief account will be of interest to workers in the tropics, where Malta fever also occurs.

Epidemiology.—Malta fever is met with at all seasons of the year in the Mediterranean, but there is a very marked increase of the disease in the hot dry season lasting from May to October, reaching a maximum from July to September and declining soon after the rainy season commences in October, although the fall is not as rapid as might have been expected if the connexion between the two were very intimate. A possible co-relation-ship to a warm temperature and to dust is indicated by this seasonal distribution. The disease is relatively more frequent among officers than among the men of the army and navy. One attack appears to protect against a second over a long period. According to Hughes all ages are liable to the disease, but infants rarely suffer, and children under 6 and adults over 50 are relatively exempt. The disease is widespread in the villages of Malta as well as in the towns.

The Occurrence of the *Micrococcus melitensis* outside the Human Body.—The mode of escape of the organism from the body is the first point to be determined in the extra-corporeal stage of its existence. The Commission have carefully studied the question, and Kennedy found the micrococcus in the spleen, liver, kidneys, lymphatic glands, blood and bile, but not in the intestines. The organism could not be recovered from expired air, saliva, sputum, sweat or scrapings from the skin. Horrocks failed to recover it from the faeces, but it may possibly escape in small numbers by the bowel as it occurs in bile. Horrocks found the organism in small numbers in the urine between the fifteenth and the eighty-second days of the disease, and Kennedy obtained it in the same way in 54 per cent of the cases he examined between the twenty-first and two hundred and forty-ninth days of the fever. From 3 to over 1000 cocci were obtained per cubic centimetre of urine, while in two cases they were innumerable. The urine, therefore, would appear to be the principal vehicle for the escape of the organism from the human body.

The Blood also contains the coccus in small numbers, it having been obtained from the peripheral circulation in from 54 to 82 per cent of cases by different observers. It may thus reach the stomachs of mosquitoes and other blood-sucking insects, but Bruce

thinks this an unlikely mode of infection on account of the small numbers found in the peripheral circulation, which rarely reach 100 per cubic centimetre.

The micrococcus of Malta fever has never yet been isolated from nature outside the animal body, but this may possibly be due to the great difficulties of separating it from numerous more vigorous saprophytic bacteria. Many experiments have been carried out by the Commission to ascertain its resisting powers under experimental conditions outside the body. In water it may survive for from six to seventy-three days, and nearly as long in sea as in tank water; here it does not multiply, but rather tends to die out. In naturally infected urines Kennedy found it could be recovered after from one to sixteen days. In non-sterile street dust inoculated with the micrococcus Horrocks recovered the organism up to twenty-eight days, but from manured garden soil only after five days. From street dust, sterilized or unsterilized, watered with infected Malta fever urine he failed to isolate the organism. The micrococcus of Malta fever then, appears to be fairly resistant, and can live in a moist or dry state for long periods outside the body. There is no evidence, however, that it has a saprophytic existence, thriving and multiplying, under natural conditions, and Bruce thinks that when the enormous dilution of the organism in dust and the sterilizing action of the sun are considered, infection through dust is very unlikely to be at all common.

BACTERIOLOGY

Animal Infection.—The Malta Fever Commission established the important fact that 50 per cent of the goats in the island were infected with the *M. melitensis*, while 10 per cent were excreting the organism in their milk, which is thus the ordinary mode of infection. The disease has now been shown to infect naturally goats, cows, sheep, horses, mules and dogs, while in addition monkeys, rabbits, guinea-pigs, rats and mice have been artificially infected, while Dubois believes fowls in the South of France suffer from the disease. The virulence of the organism is said to be increased by cultivation in goats' milk, and is preserved for the time only by intraperitoneal passage through rabbits.

Dubois found the organism can resist lactic acid fermentation and can live in cream, butter, curds and white cheese for three months. Ripened cheeses after a month cease to be infective, but the organism has been recovered from cheese up to the fifteenth day.

***M. paramelitensis*.**—In 1912 Nègre and Raynaud in Algeria isolated from a case of Malta fever a micrococcus which only agglutinated in very low dilution with a strong Malta fever serum, but when inoculated into animals produced a strong auto-serum. They named this strain *M. paramelitensis*, and it has since been obtained by other workers from fever cases. In Algeria as many goats were infected with this variety as with *M. melitensis*.

The Mode of Infection was also tested experimentally in the following ways: Monkeys appear to be able to contract the disease from each other if in close contact,

unless precautions to prevent infection through urine or mosquitoes are taken, in which case the results are negative. Artificially contaminated dust may also convey the infection, but dust contaminated with infected urine failed to infect, so that it is very doubtful if this is a common natural mode of infection. The organisms are too scantily present in the circulating blood to allow of infection through biting insects to be probable.

A small quantity of a culture injected subcutaneously or applied to a scratch produces infection in monkeys, as does infected dust through mucous membranes of the respiratory passages or conjunctiva. The recent experiments have also shown that monkeys can be readily infected by food contaminated with the micrococcus, or by naturally infected goats' milk.

In towns the most common mode of infection is through milk and its products, but in rural districts the disease is said to be more commonly spread by direct inoculation of infected soil. A house previously inhabited by sufferers from the fever may be dangerous to newcomers. Milkwomen may be infected directly from handling infected goats and then milk. There is some evidence that the disease may possibly be conveyed by sexual intercourse, as the organism may persist in the vaginal mucous membrane. Laboratory workers have frequently been infected during their work, Nicolle reporting no less than four such cases. Infants may rarely be infected from their mothers, if they are suffering from undulant fever.

Infection through Goats' Milk has proved to be the most likely ordinary mode of infection, for while examining various animals in a routine manner it was found by the Commission that the blood of some apparently healthy goats agglutinated the specific organism of Malta fever. This led to further investigations, which showed that 50 per cent of some 1000 goats examined gave positive serum reactions, while 10 per cent of them were actually excreting the *Micrococcus melitensis* in their milk. Monkeys fed for even one day on such infected milk nearly invariably contracted the disease. That a similar mode of infection also occurs in man was demonstrated in 1905 by the infection with Malta fever of nearly all the officers and crew of a vessel which had shipped sixty-five goats at Malta for America, half of which were subsequently found to give the serum reaction, while the *Micrococcus melitensis* was isolated from several of them after their arrival in America. Again, during the last twenty years Malta fever has greatly declined at Gibraltar, until it completely disappeared in 1904, this change being coincident with the cessation of the importation of goats from Malta.

In India W. C. H. Forster has found goats in the Punjab infected with Malta fever, thus confirming the above results.

Measures to abolish the use of goats' milk in messes and in the military and naval hospitals were put into operation about the beginning of July 1906, and by the end of that year the cases had dropped to broadly one-tenth of what would have been their normal number. Further, although previously one-third of the cases of Malta fever in the navy could be traced to residence in the Malta hospital, no case has occurred during residence there since goats' milk was forbidden to be used. Table XXIV. shows the monthly ratio per thousand strength of Malta-fever cases for the years 1899-1905 and for 1906 respectively.

TABLE XXIV.—MONTHLY PREVALENCE RATIO PER 1000 STRENGTH OF MALTA FEVER, EXPRESSED IN TERMS OF AN ANNUAL RATIO

	January.	February.	March.	April.	May.	June.	July.	August.	September.	October.	November.	December.
1899-1905 . . .	24.6	23.8	22.4	23.4	32.4	40.6	46.4	63.0	68.2	48.1	34.0	23.7
Quarterly prevalence .		23.6			32.1			58.9			35.3	
1906 . . .	30.9	12.6	22.7	29.2	59.4	42.3	16.4	13.9	15.7	4.0	6.5	4.1
			22.2		42.5			15.4			4.8	
1907. Total cases .	2	1	1	1	1	2						

Total for half-year : 8 cases among about 6000 men.

I am indebted to Colonel D. Bruce, R.A.M.C., for the figures for the first half of 1907, which shows only 8 cases of Malta fever in the entire garrison, averaging about 6000 persons. The disease has, therefore, practically disappeared within the last year.

Thus, as a result of a systematic inquiry by a number of scientific workers a discovery of the greatest practical importance has been made, of which years of clinical studies never even appear to have raised a suspicion : an example of the value of scientific work should lead to the expenditure of far more public money on such inquiries than has hitherto been the case.

CLINICAL DESCRIPTION

A clinical description of Malta fever as seen in India, based on an analysis of notes of a considerable series of cases is still wanting, so the following account of the disease is mainly based on Hughes' monograph.

Types of Malta Fever.—The course of the disease is so variable that Hughes found it convenient to divide it up into three main types, between which intermediate forms occur leading from one to the other.

1. **The Malignant Type** is the most acute variety, often commencing suddenly and causing death in from five to twenty-one days, sometimes with hyperpyrexia, or passing into the undulatory form. The temperature is commonly of the high continued type, and may reach 104° or 105° , closely resembling the chart of typhoid. There are epigastric, splenic and hepatic tenderness, hypostatic congestion of the lungs or basal pneumonia, offensive breath, and sometimes frequent offensive loose brown motions. The temperature seldom remains of the high continued type for more than a week or ten days, but tends early to become markedly remittent, in which it differs from typhoid, but the "typhoid state" may be well marked in the worst cases. This malignant type is fortunately rare.

2. The Undulatory Type is the commonest variety of the disease. It shows intermittent waves or undulations of more or less remittent pyrexia, of variable length, separated from each other by periods of temporary abatement or absence of symptoms. The duration of the fever varies from twenty to three hundred days, the average being sixty days and the stay in hospital ninety days. At its height the remittent temperature reaches 103° to 105° , but after a time it gradually declines, so that it is normal in the morning and but slightly raised in the afternoon, but after a few days it begins to rise once more to form a second remittent wave. This is repeated again and again, with a tendency for the waves in any given case to resemble the primary one, but generally decreasing in length and severity as the case progresses. The waves average ten days in length, while in only one-fourth of them did the average exceed three weeks. The number of waves varied from one to seven and averaged three, while the intervals varied from one to ten days, and averaged between three and four. The typical temperature chart is, therefore, a series of waves or undulations of remittent and intermittent pyrexia.

CHART 27



Malta fever from a case in Lahore, Punjab. Serum reaction positive in a dilution of 1 in 320 on the nineteenth day.

Chart 27 illustrates Malta fever in the Punjab, India; for this I am indebted to Major O. B. Sutherland, I.M.S.

3. The Intermittent Type, beginning insidiously and running a shorter and milder course than the previous types, with intermittent fever varying from normal to 100° in the morning, up to from 99° to 101° or more in the evening. This intermittent fever of a hectic type, but without any initial rigor, may continue for months with no other symptoms except night sweats, constipation and increasing debility and anaemia. If the temperature is taken frequently so as to record the daily highest point, it will be found that slight undulations take place also in this intermittent type.

The general symptoms are the following: The onset is usually insidious, and accompanied by lassitude; but rarely the dull heavy look of typhoid. Decubitus is lateral, except in very severe cases. There is no rash, but sudamina, prickly heat or boils may appear. A disagreeable or offensive odour from the skin and breath is nearly always present; the hair may fall out extensively, but not permanently, and the nails become grooved. There is copious acid sweating with each marked remission or intermission, especially at night. Pains in the back or all over, and headache, usually frontal,

but sometimes occipital, are complained of, while in 75 per cent of the cases neuralgic pains are experienced as symptoms or sequelae, usually at a late stage of the disease, such as facial or cranial neuralgia, lumbago or sciatica. Hughes has also recorded slight paralysis, without loss of reflexes, as a very rare complication.

Joint Symptoms.—In no less than 40 per cent of the cases an acute or subacute effusion into one or more joints occurs, usually commencing suddenly without any apparent reason. The acute affections occur somewhat early in the disease and usually attack only one joint, most commonly the shoulder, hip or knee. Swelling and effusion into the joint, without redness, but with excruciating pain on the slightest movement, or even at rest, are present; these require fomentations and morphia for their relief, and salicylates have little or no good effect. The acute symptoms subside in a few hours, and the swelling and pain disappear in three or four days, but may recur in another joint. The subacute form occurs late in the undulant form of the disease, or early in the intermittent type, as an effusion into one or more joints, accompanied by a slight increase of the pyrexia, and tending to pass from the larger to the smaller joints, such as the phalangeal of the hand or foot. Neither suppuration nor ankylosis ensues in either form, but stiffness may remain for weeks or months. Joint symptoms are said to be more frequent in those who have previously suffered from rheumatism. They may follow a chill, and are less frequent in those patients who wear flannel next the skin.

Circulatory System.—Hughes saw fatal pericarditis in 2 cases. This was not recognized until the patient was dying, although 15 to 17 oz. of fluid was present at the autopsies, without any lymph deposit, the onset having been insidious. The pulse may be slow, relatively, to the temperature and respirations at first, but becomes rapid in malignant or long-continued cases, when haemic murmurs may also accompany anaemia. Swelling and oedema of the legs is common during early convalescence. Endocarditis may also rarely occur. One such case was mistaken for infective endocarditis until blood culture showed the *M. melitensis*.

The Spleen nearly always extends below the ribs, and is often much enlarged and tender in malignant cases. After the second month of long attacks it frequently shrinks again. Slight swelling of the lymphatic glands without suppuration, especially in those of the neck and groin, also occurs. Great enlargement of the spleen was noted by Cartani after six months' or more fever in 6·6 per cent of his cases.

Respiratory System.—**Epistaxis** rarely occurs in the early stages. The **lungs** frequently show signs of bronchitis, usually about the beginning of the third week, with frothy or viscid expectoration, which may persist to some extent throughout the pyrexial periods. Later, in 95 per cent of the cases, some hypostatic congestion appears, which in malignant cases goes on to lobular consolidation and hypostatic pneumonia, which latter plays a large part in producing fatal results. In some cases only a few rhonchi or crepitations may be present at the apices, which, together with the hectic temperature and the night sweats, may lead to an erroneous diagnosis of early phthisis. Cough without physical signs, and a form of dry pleurisy producing adhesions, or one with slight effusion, may be met with.

Alimentary System.—The tongue is thickly coated on the dorsum, with pink edges, but without the raw red appearance of typhoid. Its condition varies roughly in proportion to the pyrexia, and it is rarely quite clean until the fever finally ceases, but remains lightly furred in the temporary apyrexial periods. Strachan in South Africa lays stress on the diagnostic value of a tongue red at the tip and edges and elsewhere covered with a light silvery fur. A subnormal temperature for a few days with a clean tongue is an almost sure sign that the disease has really come to an end. Loss of appetite, foul taste in the mouth, feeble digestive powers and epigastric tenderness nearly always occur. Occasionally nausea or even vomiting is met with. The iliac tenderness of typhoid is absent. Tympanites is also rare and seldom marked.

The Liver is often slightly enlarged and tender, both early in severe cases and towards the end of prolonged attacks, a nutmeg congestion occurring in the latter class. Late in the disease enlargement of the liver, with jaundice and ascites, has been noted by Cantani and others.

The Bowels were constipated in 81 per cent of Hughes' cases, this being the rule in non-malignant forms. Diarrhoea is common in malignant cases, and occurred in 4 per cent of the total. The bowels were normal in only 12 per cent, while in the remaining cases there was constipation alternating with diarrhoea. The association of diarrhoea with severe cases is shown by the fact that it occurred in 13 out of 22 fatal cases, usually as frequent loose, light, offensive, watery, but very rarely pea-soupy stools, dependent on marked congestion of, especially, the large bowel. The mesenteric glands may be enlarged, and in animals infected by feeding they contain the specific organism.

Urinary and Sexual System.—In the early stages with much sweating the urine may be decreased and high-coloured, but inclines to the opposite condition later. Albumen is rarely present, even in fatal cases. The fever does not produce abortion.

Epididimitis and Orchitis occur in about 4 or 5 per cent of cases as a late symptom. In the more acute form it produces very painful swelling, with some effusion into the tunica vaginalis, subsiding in a few days to leave the organ slightly enlarged and tender. A subacute form also occurs with enlargement of the epididymis and slight tenderness, subsiding in a few days under rest and support.

Other Complications.—Cold abscesses, resembling tubercular disease, occur and were noted by Strachan in South Africa in 1·8 per cent of his cases. Various cerebral conditions may arise, including meningitis, cerebritis and cerebral irritation, chorea and psychoses. Gabbi records hyperpyrexia, non-organic angina pectoris and multiple chronic muscular spasms, the last proving fatal. Two cases of phlebitis in female patients have been reported by Cantani, while painful periosteal swellings may occur.

In females Lafont has frequently seen ovarian pains, dysmenorrhoea, amenorrhoea and metorrhagia. In pregnancy there is greater danger of haemorrhage during labour. The *M. melitensis* may persist for long in the vaginal mucous membrane, making infection during intercourse possible, a danger which Eyre lays stress on. Inflammation of the mamma has also been recorded.

In Young Children.—Williams in 1917 first found the *M. melitensis* in the milk of a nursing woman, and Eyre confirmed the observation. Lura has recorded three cases of the fever in infants at the breast, whose blood agglutinated the micrococcus in high dilution, while Barton in Peru and Longo in Catania have seen a number of cases in infants, although the disease is said to be more common in children between one and three years of age than in those of less than one year.

The Blood.—According to D. Bruce and P. W. Bassett-Smith there is a moderate degree of secondary anaemia in the later stages of Malta fever, amounting to a loss of from 20 to 40 per cent of the red corpuscles. The white corpuscles show little change in their total numbers, being slightly high according to some, but Bassett-Smith never found more than 6600. The differential leucocyte count shows a decrease of the proportion of the polynuclears, and an increase of the mononuclears, including the large forms, the total proportion of both large and small having varied from 26 to 76 in Bassett-Smith's cases.

The absence of any marked reduction of the white corpuscles is thus an important guide in the distinction of Malta fever from kala-azar, but the differential leucocyte count is of no help in this respect.

Diagnosis.—The clinical diagnosis is often very difficult, especially in tropical countries, where so many fevers are prevalent. The acute malignant type is especially likely to be mistaken for typhoid, and in the early stages the cultivation of the causative organism from the blood is the only certain method of diagnosis. The undulatory type is more likely to be mistaken for kala-azar in countries where that obscure fever occurs, this error having once been made in Assam partly as a result of erroneous agglutination tests. The chronic intermittent type of fever may be thought to be tubercular disease or the "Low Fever" described on page 205.

The Serum test is the most generally useful and available method of diagnosis, but great care and precaution are necessary in carrying it out to avoid the numerous pitfalls by which it is beset. Very divergent opinions have been recorded by different laboratory workers regarding the degree of dilution which may be relied on to give reliable results, from 1 in 10 of Birt and Lamb to 1 in 16 of some writers, while between these extremes we have Eyre, who advises dilutions of 1 in 30 and 1 in 50, preferably the latter, within half an hour using a clear serum and a twenty-four-hour culture, and putting up a long series of dilutions, as some serums clump in the higher, but not in the lower ones.

Bassett-Smith from a long experience advises the following precautions: A strong emulsion is made of a forty-eight-hour agar growth of a stain with known agglutinable power, and after any auto-clumps have settled, the upper part is pipetted off. Two tubes of serum are used, one of which is heated to 57° C. for half an hour to destroy auto-agglutinines as recommended by Nègre and Raynaud, and the other is unheated. Both are put up in dilutions of 1 in 40, or 1 in 100 and 1 in 400 by the microscopical and the sedimentation method, incubated for two hours and noted, and then set aside in the cold for twelve hours and read again. Controls should always be put up with a known specific serum and a normal blood. Widal is said to use an emulsion killed with two

drops of formalin to 5 c.c., which acted well for over a year. The occurrence of the *M. paramelitensis* should be borne in mind, and this strain also used in suspected cases which fail to agglutinate with Bruce's organism, the *M. melitensis* proper. The reaction persists during fever and for some time after.

A complement fixation test may be used to supplement the serum test, as recommended by Misseroli, although not quite so reliable as the latter. A precipitin test has also been advocated, but according to Bassett-Smith is less reliable than the foregoing.

Cultivation of the Micrococcus from the Blood and Urine.—The most reliable diagnostic test when available is the cultivation of the causative organism from the blood, which is most frequently successful in comparatively early stages of the fever, when the clinical diagnosis may be most open to doubt, while success has been obtained as late as a year after the fever began. About 5 c.c. of blood are removed from a vein with a sterile syringe containing a few drops of 10 per cent citrate of soda, preferably late in the day when the temperature is raised, as advised by Eyre, and placed in a flask of about 50 c.c. of broth, subcultures being made on agar from the third to the tenth day. The agglutinating properties of any cocci obtained should be tested with *M. melitensis* and *M. paramelitensis* sera. Cultures may also be made from the spleen blood obtained by puncturing the organ, but the possible dangers of this operation must be considered before this is done. In some cases the organism can be cultivated from the urine, such patients being potential carriers of the disease.

Treatment.—No drug is known to have any definite influence in checking the course of the fever. De Brun has advocated daily hypodermic injections of $2\frac{1}{2}$ grammes of the neutral hydrochlorate of quinine, smaller doses being of no use. In infected animals Scordo has given perchloride of mercury intravenously in goats with success, while Izar has used ethyl-copper-chloride intravenously in rabbits in doses of .05 gramme in a watery solution with 68 per cent of successes if given within the first nine days, but not later. Bassett-Smith advises yeast. For the pain bromides or phenacetin and caffeine may be given, and belladonna and opium applied over the joints, best in the form of fomentations. Trional and other hypnotics may be required for sleeplessness.

A serum was made many years ago by Sir Almroth Wright, but this line of treatment has been found useless by most observers. Trambusti and Donzello have prepared a serum by inoculating goats with a nucleo-proteid derived from the *M. melitensis* which gave them satisfactory results if used early in the case.

Vaccines have been largely used with varying success. In such a long fever with ultimate spontaneous recovery it is difficult to estimate the value of a vaccine treatment, but Bassett-Smith and some others have recorded favourable results in subacute cases more especially. An autogenous vaccine in doses gradually increased from 100 to 500 millions is most likely to succeed. Sensitized vaccines have also been recommended.

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VIII. THE PRE-SUPPURATIVE STAGE OF AMOEBOIC HEPATITIS

ITS EARLY DIAGNOSIS AND CURE

No one who has had a large experience of the early stages of amoebic abscess of the liver in a tropical climate can fail to have been struck by the great frequency with which definite clinical symptoms of suppuration in this organ are preceded by weeks or even months of fever, during which there may be few if any symptoms pointing to the liver as the cause of the trouble; this fever is commonly ascribed to and treated as "malaria." Moreover, even when marked symptoms of acute hepatitis are present it is frequently impossible to decide whether an abscess has already formed or not without resort to an exploratory operation, which only too often gives a negative result in cases where an abscess of the liver is found at a later date.

In a paper published in 1905 I discussed the value of leucocytosis in acute hepatitis, and concluded that its presence in a marked degree was generally an indication that suppuration had already taken place, but that in the slighter degrees it may be present in acute hepatitis without actual suppuration, and that this early stage of amoebic hepatitis may sometimes be cured, and suppuration prevented, by the administration of large doses of ipecacuanha. Since then I have repeatedly confirmed this observation. I can now go a step in advance of that position.

During the last two years in the course of this investigation of fevers in Calcutta I have met with a most interesting group of cases, which appear to me to throw much light on the early pre-suppurative stages of amoebic hepatitis, and indicate that this disease may frequently be recognized by the blood changes when in a stage which admits of rapid cure; thus the patient is prevented from drifting on into the much more serious suppurative stage, now so commonly their fate. Further, these cases constitute a distinct class of fever, usually of a chronic intermittent type, sometimes with no very definite symptoms of hepatitis, and rarely with any dysentery. They may be recognized, or at least strongly suspected, by the presence of a moderate degree of leucocytosis, generally of the type which I have described as common in amoebic abscess of the liver, namely, one in which the proportion of polynuclears is either normal or only slightly in excess. Further—and this is the most important practical point—this kind of fever yields rapidly to large doses of ipecacuanha in the absence of symptoms of dysentery, or even of hepatitis, and the formation of tropical abscess of the liver is thus prevented. If this proposition can be substantiated a great advance will be made in the prevention of one of the most dangerous diseases of certain tropical countries; it will therefore be well to give notes and charts of some of the data on which the above statements are based.

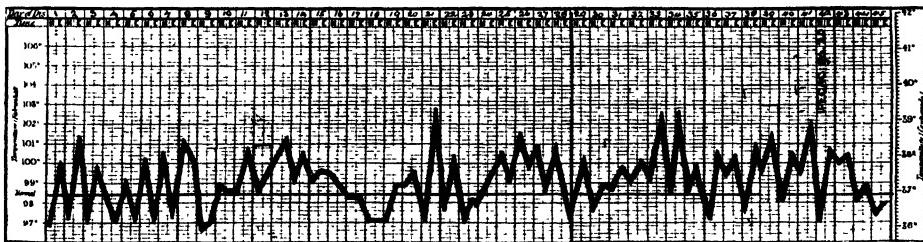
For convenience of reference all the cases of non-suppurative hepatitis met with in the Calcutta European Hospital fever series during the year subsequent to those dealt with in my 1905 paper on blood counts in amoebic hepatitis have been embodied in Table XXV. and classed in accordance with, whether they showed clinical symptoms of dysentery and hepatitis, hepatitis alone, or no definite signs of either at the time the blood examination was made. The patients were under the care of Drs. B. Chatterton, J. C. H. Leicester and J. G. Murray, all of the Indian Medical Service, to whom I am greatly indebted for permission to examine the blood and make use of the hospital notes.

I. CASES OF ACUTE HEPATITIS COMPLICATED WITH DYSENTERY

Beginning with the simplest and most straightforward cases, we first have Nos. 1 to 3, in which an acute hepatitis followed symptoms of dysentery, leucocytosis being present in each, while as the liver was also enlarged and very tender, liver abscess was suspected, and in No. 3 exploratory puncture of the liver in six places was done with a negative result. In all three cases the ipecacuanha treatment was followed by cessation of the fever and other acute symptoms within from two to four days, although they had been present for fifteen, thirty-four and forty-one days respectively before this drug was given in large doses. The following are the principal points of interest in these cases.

Case 1.—A male, aged 38, who had been in hospital two and a half months previously for a slight attack of hepatitis, which yielded to ammonium chloride treatment in three days. He had suffered from dysentery on and off for seven months before this first attack of hepatitis, and on readmission was passing mucus and blood, but showed no sign of hepatitis. The dysentery improved under bismuth, but the irregular intermittent fever

CHART 28 (Case 1)



European, male, aged 38. Dysentery followed by hepatitis. Fever forty-one days before and for two days after ipecacuanha treatment.

continued in spite of quinine, and one month after he came into hospital I found slight increase of the leucocytes not amounting to an actual leucocytosis. Six days later, his liver having become tender, a second examination showed 15,250 white corpuscles per cubic millimetre, a leucocytosis having now developed. Although all active symptoms of dysentery had long ceased, I suspected a latent form of the disease as the cause of the hepatitis, and advised the ipecacuanha treatment, which was followed by a permanent

TABLE XXV.—BLOOD COUNTS AND IPECAUANHA TREATMENT OF PRE-SUPPURATIVE AMOEBOIC HEPATITIS

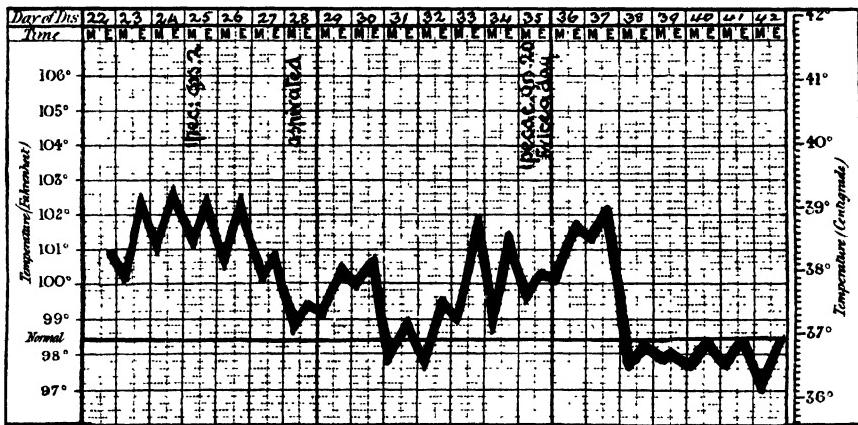
No.	Sex.	Age.	Bowels.	Liver. Inches below Costal Margin.	Days' Fever before Ipe- cauanha Treatment.		Red Corpuscles.	White Corpuscles.	Ratio White to Red.	Poly-nuclear. Leucocytes.	Large mono- nuclear. Leucocytes.	Bosmophiles.	Remarks.
					Days' Fever after Ipe- cauanha Treatment.	Tender							
I. CASES WITH DYSENTERY AND HEPATITIS TREATED WITH IPECAUANHA													
1	M.	38	Dysentery	1	41	2	3,600,000	15,250	1-236	83	13	4	0
2	M.	31	"	2½	"	15	4	..	Leucocytosis	..	78	16	2
3	M.	33	"	1½	"	34	3	79	12	6	3
II. CASES OF HEPATITIS WITHOUT DYSENTERY NOT TREATED WITH IPECAUANHA													
4	M.	38	Normal	½	Tender	49	..	3,090,000	24,000	1-129	78	15	7
5	M.	45	"	2	"	39	..	3,610,000	28,500	1-126	76	21	3
6	M.	34	"	½	"	34	..	3,960,000	9,500	1-416	78	8	3
III. CASES OF HEPATITIS ONLY WITHOUT DYSENTERY TREATED WITH IPECAUANHA													
7	M.	40	Irregular	1½	Tender	15	1	4,820,000	21,000	1-230	78	15	5
8	M.	38	Normal	1	"	14	4	4,600,000	17,750	1-233	87	7	5
9	M.	31	Diarrhoea	0	"	25	5	..	Leucocytosis	..	80	15	4
10	M.	35	Constipated	2½	"	50	5	5,380,000	17,000	1-316	76	16	2
11	M.	38	Normal	0	"	13	6	4,910,000	9,500	1-517	79	16	4
IV. CASES WITHOUT DYSENTERY OR LIVER SYMPTOMS TREATED WITH IPECAUANHA													
12	M.	40	Normal	1	Normal	6	..	4,290,000	15,250	1-272	81	11	7
13	M.	28	"	¼	"	53	15	..	Leucocytosis
14	M.	24	Irregular	1	"	35	2	4,660,000	20,750	1-225
15	M.	32	Constipated	0	"	45	12	3,340,000	17,250	1-193	74	22	3

cessation of the fever within two days, as seen from Chart 28, although the case was just one of those which ordinarily drift on into liver abscess.

Case 2.—This man was also admitted for dysentery, together with signs of acute hepatitis and a leucocytosis, but the remittent temperature fell to normal in four days under ipecacuanha, although there was a slight relapse of the dysenteric symptoms four days later, but at the end of sixteen days the fever finally left him. A Widal test with Shiga's bacillus gave a negative result in a dilution of 1 in 20, so the dysentery was probably amoebic in nature. This case was a straightforward one of dysentery followed by hepatitis yielding to the well-known ipecacuanha treatment as advised, when dysentery is present, by Sir Patrick Manson and other authorities.

Case 3.—A male, aged 33, whose illness began three weeks before admission with dysentery, lasting for two weeks. He was passing loose greenish stools, his liver was enlarged and tender, and leucocytosis was present. X-rays showed loss of movement of the diaphragm on the right side, and, liver abscess being suspected, the organ was punctured in six places under chloroform with a negative result. He had been given ipecacuanha in 2-grain doses, with only some lessening of the pyrexia resulting, but two weeks after admission he was given 20-grain doses twice a day, and on the third day his temperature finally fell to normal, and he rapidly recovered (Chart 29).

CHART 29 (Case 3)



European, male, aged 33. Hepatitis following dysentery. Aspirated for liver abscess with negative result. Fever and hepatitis ceased in three days under ipecacuanha treatment.

Remarks on Group I.—These three cases illustrate the well-known treatment of cases of dysentery complicated by acute hepatitis, by large doses of ipecacuanha, although the rapidity with which the hepatitis with a definite leucocytosis yielded to the drug in spite of the dysenteric symptoms being in abeyance in two of them is noteworthy, for

it is just such cases which so commonly drift on into the suppurative stage of the disease if this treatment is neglected, as it too often is in the tropics at the present day.

II. CASES OF HEPATITIS WITHOUT DYSENTERY NOT TREATED WITH IPECACUANHA

Next I come to cases of acute hepatitis without any recent dysentery, 8 in number, which I have divided up into those treated with large doses of ipecacuanha and those not so treated. I will first deal with the 3 cases not treated with this drug (Nos. 4 to 6).

Case 4.—A seaman, aged 38, admitted for acute hepatitis with a leucocytosis, but no dysentery. X-rays showed reduced movement of the diaphragm on the right side, and eight days after admission the liver was aspirated in two places, only blood being obtained; the abdomen was then opened, the organ palpated, and punctured in three more places, again with a negative result. Irregular intermittent fever continued for twelve days after the operation, and a few days after the pyrexia ceased the leucocytosis was also found to have disappeared. He continued to have occasional slight rises of temperature for another month, but eventually left hospital apparently well after sixty-two days under treatment; as he went to England I was unable to follow up his case further, so that I cannot say if he eventually developed a liver abscess or not. He was not treated with large doses of ipecacuanha while in hospital, and his recovery was a very protracted one.

Case 5.—A male, aged 45, admitted for low intermittent fever and hepatitis, his blood showing a very marked leucocytosis, 28,500 per cubic millimetre; his liver was also punctured in several places without any pus being found. The pyrexia ceased after thirty-nine days, and he left hospital at his own request much improved after fifty-seven days' stay. He was readmitted for another much slighter attack of hepatitis ten months later.

Case 6.—Admitted for mild hepatitis with low intermittent fever up to about 100° only, which lasted for thirty-four days under quinine treatment without any very acute symptoms appearing. Here there was no leucocytosis, the case being probably alcoholic in origin, but it is included so as to furnish a consecutive series of unselected cases.

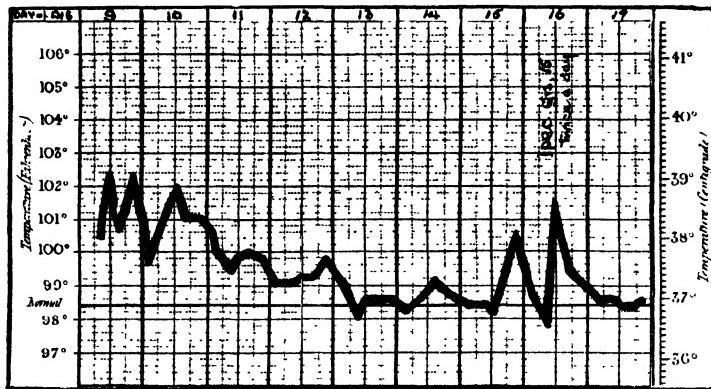
Remarks on Group II.—The first two of this group are typical of the class of acute hepatitis without dysentery, in which leucocytosis pointing to liver abscess is present, and exploratory operation becomes necessary to decide if a liver abscess has formed or not, a negative result being not uncommonly followed by a slow improvement and ultimate recovery, although they are apt to relapse and an abscess is frequently found at a later date. They will serve for comparison with the next group in which the ipecacuanha treatment was carried out.

III. CASES OF HEPATITIS WITHOUT DYSENTERY TREATED WITH IPECACUANHA

Cases 7 to 11 all presented signs of acute hepatitis without any recent dysentery. 4 out of the 5 also showing marked leucocytosis. They were all treated with ipecacuanha.

Case 7.—Had been in hospital for a short attack of hepatitis four months before. No history of dysentery, but had suffered occasionally from a watery diarrhoea alternating with constipation—a not infrequent occurrence in amoebic hepatitis. He suffered from fever for fifteen days of a low remittent and intermittent form, at the end of which he was put on the ipecacuanha treatment, and two days later his temperature finally fell to normal, and he made a good recovery, returning to work after thirty-two days in hospital. However, he returned five months later with a liver abscess, which was cured by aspiration and injection of quinine into the cavity, after which he went to work again and remained quite free from fever for eight weeks, when he returned with a second abscess in a different part of the liver from the one which had been injected with the quinine. A similar treatment was tried on the fresh abscess, but this time it failed, and eventually it had to be opened and drained. Since this he has had no return of his trouble (Chart 30).

CHART 30 (Case 7)



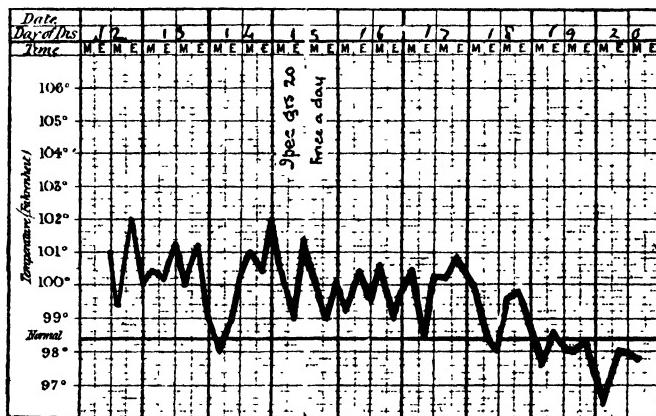
European, male, aged 40. Hepatitis without dysentery for fifteen days.
Symptoms disappeared in one day under ipecacuanha treatment.

In connexion with this method of treating early cases of liver abscess by aspiration and injection of soluble bihydrochloride of quinine into the cavity to kill the amoeba when it is found to be free from bacteria, I regret to have to report that in 3 further cases, treated by Captain J. G. Murray, I.M.S., at the General Hospital, Calcutta, it failed, and the open operation had to be resorted to. I am informed that in Bombay a similar experience was obtained in 2 cases, so that the treatment has not fulfilled my anticipation of success in most of the cases of tropical abscess. On the other hand, I have been informed of several cases in which it has proved successful in other hands than my own, so that

in view of the rapid and comparatively painless cures it sometimes effects, and its harmlessness as far as our Calcutta experience guides us in those cases which have eventually to be cut open, I still think it is worthy of trial in early, deep-seated amoebic abscesses of the liver.

Case 8.—A male, aged 38, admitted for acute hepatitis without any history of dysentery, and no present bowel trouble. His temperature showed the rapid oscillations produced by the frequent profuse perspirations so common in acute liver inflammation, a marked leucocytosis was present, and he had occasional rigors. Nevertheless, the pyrexia and all the acute symptoms yielded in four days to 20-grain doses of ipecacuanha morning and evening (Chart 31).

CHART 31 (Case 8)



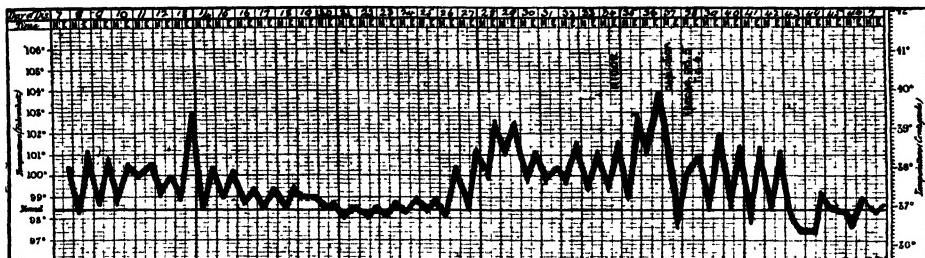
European, male, aged 38. Acute hepatitis without dysentery for fourteen days. Leucocytosis present. Hepatitis and fever ceased in four days under ipecacuanha treatment.

Case 9.—A male, aged 31, admitted with a subacute hepatitis, with low intermittent fever, watery diarrhoea, and a slight degree of leucocytosis, all the symptoms disappearing within five days of the beginning of the ipecacuanha treatment.

Case 10.—A male, aged 35, admitted for acute hepatitis with constipation and low intermittent fever, which improved for a time under quinine, only to return shortly after. A month after his admission I was asked to examine the blood, and found 17,750 leucocytes per cubic millimetre; the liver was punctured, but with a negative result. He was then put on 5 grains of ipecacuanha three times a day, and four days later was injected with antistreptococcus serum, the temperature finally falling the next day, and he made a good recovery. In this case it is difficult to say whether the happy result was due to the ipecacuanha or to the serum, but I am inclined to think it was the former, because two and a half months later he returned with an amoebic abscess of the liver, which was opened and drained with an ultimately fatal result; thus his earlier attack was pretty certainly

also amoebic in origin, and so likely to have yielded for a time to the small doses of ipecacuanha given (Chart 32).

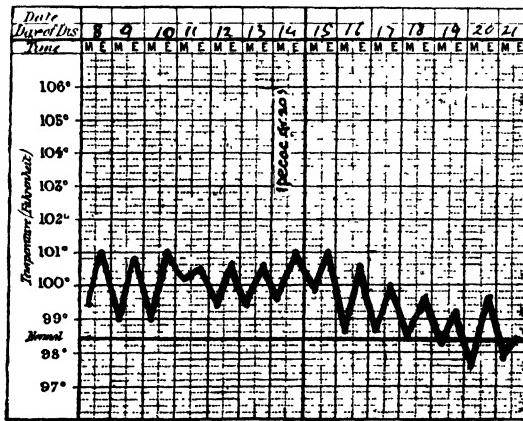
CHART 32 (Case 10)



European, male, aged 31. Acute hepatitis without dysentery for thirty-seven days. Leucocytosis present. Liver aspirated with negative result. Fever and hepatitis ceased five days after ipecacuanha treatment and one day after antistreptococcus serum

Case 11.—Male, aged 38, who had suffered from dysentery twelve years before. Bowels now normal, but symptoms of acute hepatitis without leucocytosis and low remittent fever, which declined when the ipecacuanha treatment was commenced, and finally ceased after six days, the case being a somewhat mild one (Chart 33). . . .

CHART 33 (Case 11)



European, male, aged 38. Dysentery twelve years ago only. Acute hepatitis for thirteen days, ceasing in six days under ipecacuanha treatment.

Remarks on Group III.—These cases of hepatitis without dysentery are precisely similar to those of Group II., but the pyrexia and other symptoms rapidly ceased under the ipecacuanha treatment within from one to six days, although they had previously been present for from thirteen to thirty-seven days, and in No. 10 aspiration had been

done on account of a suspicion of liver abscess being present. In short, the effect of this treatment was precisely the same as in the first three cases in which symptoms of dysentery as well as hepatitis had been evident.

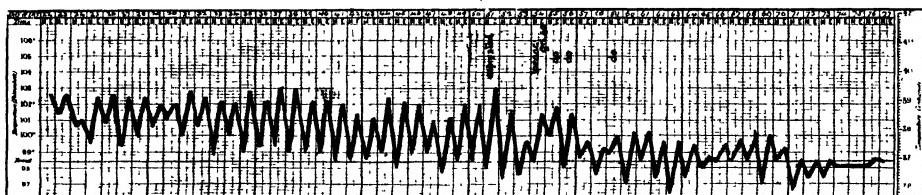
IV. CASES WITHOUT DYSENTERY OR LIVER SYMPTOMS TREATED WITH IPECACUANHA

Cases 12 to 15 all showed leucocytosis without symptoms of either dysentery or acute hepatitis being present, fever, for which no definite cause could be found, being the condition for which they were admitted. As there was no obvious cause for the leucocytosis I suspected that latent amoebic dysentery, as well as the insidious form of hepatitis, which sometimes precedes actual abscess formation, might be present. I therefore suggested a trial of the ipecacuanha treatment, which had proved so efficient in the more acute forms of amoebic hepatitis, although there was neither pain nor tenderness of the liver present when they were first admitted, in spite of slight enlargement in 3 of the 4 patients. The results were most satisfactory.

Case 12.—A seaman, aged 40, with alcoholic history, whose pyrexia ceased after six days without ipecacuanha, but who was subsequently treated with it on account of the presence of leucocytosis in order to try and prevent a recurrence of the liver trouble, as the fall of temperature might have been temporary improvement only. This case must be acknowledged to be a doubtful one.

Case 13.—Male, aged 28, admitted for fever of three weeks' duration, which persisted under quinine treatment, although no cause could be found for it. Bowels normal, both sides of the diaphragm moving well, as seen by the X-rays. Liver slightly enlarged, but not tender, although becoming larger. Leucocytosis was found by me both one week and three weeks after admission; the liver was therefore explored for abscess with a negative result. Three days later, or fifty-three days after the fever began, the ipecacuanha treatment was commenced, and on the fourth day the temperature was normal, but slight low fever up to 100° F. recurred for several days more, after which convalescence set in, as shown in Chart 34.

CHART 34 (Case 13)



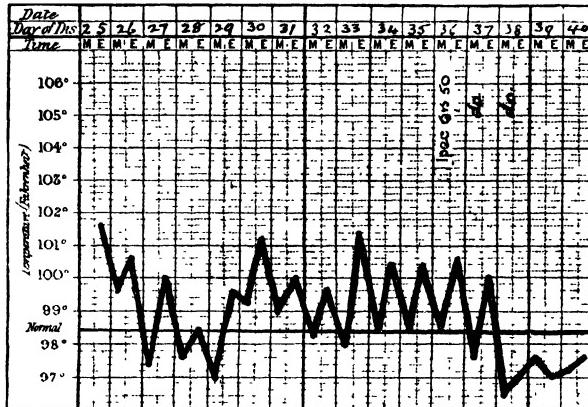
European, male, aged 28. Fever without any symptoms of dysentery or hepatitis for fifty-three days. Leucocytosis found and liver aspirated with negative result. Fever ceased in a few days under ipecacuanha treatment.

This was a most remarkable case, as the nature and cause of the fever was quite a puzzle until the presence of leucocytosis led to a suspicion that latent amoebic dysentery

and hepatitis might be at the bottom of it, while the rapid success of the ipecacuanha treatment in such a persistent fever appears to me to support the correctness of this view.

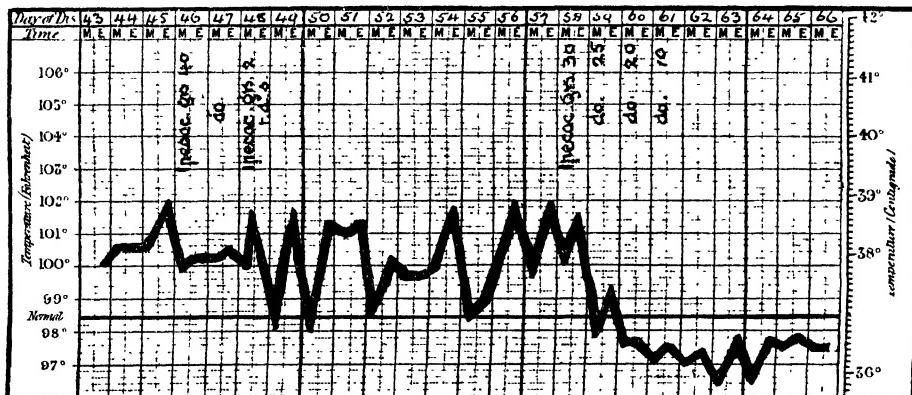
Case 14.—Male, aged 24, admitted for irregular intermittent fever, not yielding to quinine, and with no obvious cause. As over 20,750 leucocytes were found the ipecacuanha treatment was again adopted with the happiest results, the fever finally ceasing two days later, and convalescence being quickly established, as in the preceding case (Chart 35).

CHART 35 (Case 14)



European, male, aged 24. Fever without dysentery or hepatitis. Leucocytosis found. Fever ceased in two days under ipecacuanha treatment.

CHART 36 (Case 15)



European, male, aged 32. Fever without dysentery or hepatitis. Leucocytosis found, and fever ceased under ipecacuanha treatment.

Case 15.—Male, aged 32, admitted for fever with no ascertainable cause and resistant

to quinine. Bowels constipated ; diaphragm moving well. A well-marked leucocytosis was found ; 40 grains of ipecacuanha were given on two consecutive days followed by 2 grains twice a day, but with apparently very little effect on the fever.

Quinine was then tried hypodermically without result, and on the sixteenth day after admission 30 grains of ipecacuanha were again administered, and repeated in doses diminished by 5 grains each day, which treatment was followed by a final cessation of the pyrexia in two days (Chart 36). In this case the fever had lasted for forty-five days before the first trial of ipecacuanha, so that it is, perhaps, not surprising that two large doses failed to stop it, and it had to be repeated again a few days later. The ultimate result was as satisfactory as in the previous cases, so that I do not think the repeated apparently good results of this treatment can be simply a coincidence.

Remarks on Group IV.—The remarkable feature of these last four cases is that there were no bowel or liver symptoms to make one suspect the presence of amoebic hepatitis, until an otherwise unexplainable leucoeytosis was found on examining the blood. Yet on administering large doses of ipecacuanha in 3 of the cases, after the fever had resisted quinine and other treatment for thirty-five, forty-five, and fifty-three days respectively, the pyrexia and other symptoms subsided in much the same way as in the previous groups, which showed definite symptoms of hepatitis with or without dysentery. Moreover, judging from a prolonged experience of similar cases before this treatment was so commonly used in the Calcutta European Hospital, this class of patients very frequently drift on into liver abscess formation unless their true nature is discovered and the ipecacuanha method vigorously used, while I know of nothing but the presence of leucocytosis which will allow of their nature being suspected in this early stage when they are so readily amenable to medical treatment. I may add that several very similar cases seen in consultation have furnished equally satisfactory results under ipecacuanha to those dealt with above.

The following further experiences and cases illustrating different points confirm the value of the treatment of amoebic hepatitis with large doses of ipecacuanha, which I have pointed out was empirically recommended many years ago in tropical hepatitis by McClean and Norman Chevers, although it had fallen very much out of use before I revived it and placed it on a scientific basis by my researches on amoebic dysentery and liver abscess.

The views put forward above have been completely confirmed by much further experience in India. A number of instances of the success of large doses of ipecacuanha, in rapidly curing very acute hepatitis with suspected abscess formation, have been reported to me, in many of which the results were described as marvellous. At the European hospital in Calcutta this treatment has been adopted, with very satisfactory results, in twenty-five cases during 1907-8. It may now be said that in the general wards of this hospital no case has occurred during the last four years of acute hepatitis going on to the formation of liver abscess after admission, although previously this was a frequent occurrence. Still more striking is the number of patients sent from distant places, for operation for liver abscess, who completely recovered under treatment with ipecacuanha, having come under observation just in time to prevent suppuration taking place. Again, negative

results from explorations for liver abscess, which were so common in the series tabulated on page 187, have been conspicuous by their absence during the last two years, as surgical measures are not now undertaken until after a careful trial of ipecacuanha in full doses, unless there are obvious signs of abscess formation on admission. As this treatment is becoming more widely known the admission of Europeans for liver abscess is becoming less frequent. It is now not too much to say that this dreadful disease is entirely preventable, in the vast majority of cases, in those who come under skilled treatment in the early stages of acute amoebic hepatitis, and the formation of a tropical liver abscess should soon become a very exceptional occurrence, which ought to cause serious questionings in the mind of the medical man in whose hands it has been allowed to develop.

In natives of India the disease is comparatively rarely seen in hospitals in the pre-suppurative stage, owing to their having been treated by unqualified men for "fever" for weeks before seeking admission to hospital with a large liver abscess. Nevertheless, a number of cases in the pre-suppurative stage have been successfully treated with ipecacuanha by the physicians of the Medical College Hospital, especially by Surgeon-General C. P. Lukis and Colonel G. F. A. Harris, I.M.S., including several with very acute symptoms and greatly enlarged tender livers, in whom suppuration was strongly suspected. In at least two such cases I have seen actual oedema over the right lower ribs, which is usually regarded as a sign of suppuration, so the question arises whether under this treatment a small abscess may frequently subside and encyst, as is known to occur occasionally in nature. I therefore think that all cases in which the least doubt remains as to whether actual suppuration has taken place, should be given the chance afforded by a course of ipecacuanha before any operation is undertaken. Further, it is by no means rare for a patient, who has been successfully operated on for liver abscess, to return within one or more years with another abscess. I have shown that amoebic ulcers are certainly present in the large bowel at some period in over 90 per cent of tropical abscesses of the liver, and probably in all of them, although frequently in a latent condition and producing no definite dysenteric symptoms. I am therefore strongly of the opinion that every case of liver abscess should be given a course of ipecacuanha before leaving hospital, in order to cure these ulcers, and so prevent a recurrence of the very serious liver complication. If operative measures are urgently necessary, the drug can be postponed until after the patient has recovered from the immediate effect of the surgical procedures, and is in a position to stand the rather depressing influence of the large doses which are necessary. The following cases will serve to illustrate the more important of the above points.

Very Acute Hepatitis with suspected Liver Abscess following immediately on Dysentery.—European male, aged 25, admitted for dysentery of six weeks' duration. About six stools of blood and mucus daily, without pain or straining, which subsided in ten days under treatment with castor oil mixture and creolin enemas. Seven days later he began to suffer from pain in the hepatic region and right shoulder, while his temperature, which had been normal for twelve days, changed to a remittent type of fever ranging between 99° and 103° F. The pains continued to be severe, the breath sounds at the right base became diminished and profuse sweats occurred, and on the eighth day of the hepatitis the right side of the diaphragm was found by X-rays to be quite motionless,

and there appeared to be a slight shadow in the right lobe of the liver. Abscess within this organ was, therefore, confidently diagnosed by the very experienced medical man in charge, but as the patient had recently suffered from dysentery he agreed to give a few full doses of 30 grains of ipecacuanha before operating. On the following day the pain and sweating were less, and a day later the pain over the liver had entirely ceased, although it continued a little longer in the shoulder. The temperature steadily fell during the next three days, after this it remained normal and all the signs of liver abscess completely disappeared. No possible doubt remained in the minds of those who watched this patient that the ipecacuanha had averted acute suppuration in the liver.

Chronic Hepatitis yielding only to full Doses of Ipecacuanha.—European male, aged 29, admitted for hepatitis. Had dysentery two and a half months before in Singapore. He was first treated with ammonium chloride and quinine without good effect. Then 5-grain doses of ipecacuanha stopped the fever in two days, but it recurred after a week. Salines, aspirin, salol and bismuth were tried in turn without any good results. Six weeks after admission he was put on 30-grain doses of ipecacuanha every evening, which immediately reduced the temperature to a low intermittent type, and it finally ceased, together with all other symptoms, after fourteen days, and remained normal during the further month he remained under observation in hospital. This case shows the necessity of using full doses of the drug for a considerable period in chronic persistent amoebic hepatitis.

Mild Hepatitis yielding to other Drugs which relapsed very severely Three Months later.—European male, aged 26, admitted in the month of August for hepatitis following dysentery. Under treatment with podophyllin and euonymin the symptoms and fever slowly abated in fifteen days, and he left hospital soon after. He returned just three months after his first admission and gave a history of having had fever every evening, beginning a month after leaving hospital, with rigors and sharp pain in the hepatic region at times. The liver extended from the fifth space to four inches below the costal margin, and there was slight bulging and tenderness over the organ. The breath sounds were diminished at the left base, and X-rays showed the right arch of the diaphragm to be two inches higher than the left, hardly moving at all, even on deep respiration, but there was no denser shadow in the liver. The temperature was ranging between normal and 103°. Liver abscess was suspected, but a trial was given of ipecacuanha in 30- to 40-grain doses every evening. The day after admission I found the leucocytes to number 15,000 per c.c., with only 76.8 per cent of polynuclears. He slept well the night after the first dose of ipecacuanha, and the following morning the pain was less, and he could turn over on to his right side for the first time. Two days later the tenderness over his liver had disappeared, although the temperature still rose to 103° in the evenings. On the fifth day after the commencement of the treatment the temperature became normal and so remained, all acute symptoms having subsided. The liver slowly decreased in size, reaching two and a half inches below the ribs on the twelfth day, and one and a quarter on the seventeenth day, and was only just palpable on the thirty-third day, when he was quite well. I am indebted to Captain J. G. Murray for the notes of this case and for the opportunity of watching his progress. It very well illustrates the usual sequel of events

in acute cases treated by ipecacuanha. First the pain diminishes, then the temperature rapidly or gradually subsides, and lastly the liver decreases in size and the right side of the diaphragm regains its lost mobility.

Chronic Fever of Doubtful Nature yielding to Ipecacuanha but relapsing on early Cessation of the Drug.—European male, aged 29, admitted for fever with history of dysentery of a week's duration one month before coming to hospital. No rigors. Fever of intermittent type. Slight pain and tenderness in the right hypochondrium, where the edge of the liver could be felt half an inch below the ribs. Other organs normal and the bowels regular. He was treated with quinine by the mouth, iron and arsenic, and quinine hypodermically in turn for a period of six weeks, at the end of which time the temperature was rising higher, reaching 102° in the evening, and slight pain had appeared in the left shoulder, but the diaphragm moved well on both sides. He was now put on 60 grains of ipecacuanha for two days, and 30 grains for five more. The temperature immediately began to decline steadily, and remained normal on the fourth day, and he felt better. Six days later the temperature began to rise daily to between 99° and 100° F., and at the end of two weeks more it rose once more to 102°, when he was again put on 30-grain doses of ipecacuanha daily, and the fever finally left him two days later.

Three Cases sent to Hospital for Operation for Liver Abscess, but cured with Ipecacuanha.—Three cases were of special interest, as the patients were all sent many hundreds of miles to the Calcutta European Hospital for operation for liver abscess, which had been diagnosed, not without good reason, by their doctors, on account of the very acute hepatitis present. The third had begun a course of ipecacuanha a few days before his arrival, and was already slightly better as regards the acuteness of the pain. Nevertheless, he had a marked leucocytosis with high and fixed right diaphragm and increased opacity of the liver shadow. Abscess was therefore suspected, but fortunately all the symptoms, leucocytosis and loss of movement of the diaphragm rapidly subsided under full doses of ipecacuanha, and I heard of his being still well over a year later. The first patient was sent down from Allahabad for very urgent operation for liver abscess, and the hospital staff sat up to 12.30 A.M. in readiness for surgical procedures on his arrival. A brief examination led to the conclusion, suggested by previous experience, that the acute symptoms might still possibly subside under medical treatment, although there were very strong reasons for thinking an abscess of the liver might be present. He was given the benefit of the doubt, and all the alarming symptoms subsided in a few days under ipecacuanha. In Case 11 the symptoms were less urgent, but the medical treatment was equally happy in averting the necessity of a serious operation. The second case was noteworthy for the presence of distinct bulging of the lower ribs over the enlarged and tender liver causing abscess to be strongly suspected, but the temperature rapidly fell under the usual ipecacuanha treatment, and the liver steadily subsided.

Acute Hepatitis with Dense Shadow in the Liver slowly subsiding under Ipecacuanha.—European male, aged 33, admitted for hepatitis following an attack of dysentery ten days before. The liver extended from the level of the right nipple to just below the edge of the ribs, and he had pain over it. X-rays showed the right diaphragm to be high and

quite fixed, while there appeared to be a dense shadow in the upper part of the right lobe. Poultices were applied to the side and ipecacuanha was given in 20- to 30-grain doses daily. Three days later the temperature was lower, but the diaphragm equally fixed, although no shadow was made out. Low fever rising to 100° F. in the evening persisted, but seven days after the last note the diaphragm was found to move 1 inch on the right side, and no shadow appeared. On the fifteenth day the temperature fell and remained normal, and a fortnight later the diaphragm had regained about its full movement. The slow subsidence of the fever, together with the presence of a shadow in the liver, suggested the possibility of a localized abscess having been present, which encysted under the treatment adopted. Even a shadow in the liver is not, however, conclusive evidence of an abscess in the organ, as proved in another recent case at the same hospital, while the absence of one is not proof that no localized suppuration has occurred, so that this case is only suggestive of encystment of an abscess clinically observed having taken place. It at least illustrates the importance of giving a prolonged trial to the drug in cases of hepatitis which fail to yield as rapidly as the general run do.

Chronic Hepatitis rapidly cured by Ipecacuanha after Failure of other Drugs.--European male, aged 29, admitted for chronic hepatitis of six months' duration, but much worse for the last seventeen days, with slight fever, sweats and pain over the liver and in the right shoulder. He was treated in hospital with sodium sulphate and ammonium chloride, arsenic and dilute hydrochloric acid for thirty-one days, with very little result, his temperature being higher at the end of this period than on his admission. He was now put on ipecacuanha in 30-grain doses every evening, and his fever finally ceased in five days.

Acute Hepatitis with Involvement of the Base of the Right Lung clearing up under Ipecacuanha.--European male, aged 43, admitted with a history of fever for one month, with severe pain over the liver during the last few days. The liver extended from the sixth rib to one inch below the costal margin. Temperature from 100° to 102° F. X-rays showed the diaphragm on the right side to be high and nearly fixed, while the base of the left lung was darker than normal and the outline of the diaphragm blurred. No shadow in the liver. There were also a few crepitations to be heard at the base of the right lung. An abscess was suspected at the upper part of the liver, with spreading of the inflammation to the base of the right lung, but he was put on ipecacuanha in the hope that suppuration might not actually have taken place. On the following day the pain over the liver was much less, but the temperature only very slowly declined to some extent during the first six days. At the end of this time X-rays showed the right side of the diaphragm to be moving almost as well as the left, while the opacity at the base of the left lung had almost gone, leaving the vault of the diaphragm clearly defined. On the eighth day the temperature remained quite normal, but the first and third days after this a high intermittent rise occurred, which proved to be benign tertian malaria, which yielded at once to quinine, and he made a complete recovery.

Acute Hepatitis developing Suppuration in Hospital without Ipecacuanha Treatment.--The patient, a European, was admitted for fever of three weeks' duration, of uncertain

nature. A few days later signs of acute hepatitis developed and leucocytosis being also found an exploratory laparotomy was performed, on account of the left lobe of the liver being much enlarged and very tender. The liver was palpated and repeatedly aspirated with a negative result. Ammonium chloride and saline purges were accordingly continued, and the temperature was lower for a time. Four weeks after his admission the fever again became higher, and on the thirty-eighth day in hospital a second operation was performed, and an abscess opened in the very part of the left lobe of the liver which had been proved to be free from suppuration at the first operation twenty-nine days before. The case terminated fatally. He had never had any ipecacuanha, the routine treatment with ammonium chloride and large doses of quinine having been used in accordance with the general teaching of recent times. Yet this patient showed far less urgent signs of hepatitis when first admitted than the great majority of the cases which cleared up so readily under the ipecacuanha treatment. I venture to think that such misfortunes will become increasingly rare with the growing use of the treatment here advocated.

DURATION OF THE READILY CURABLE PRE-SUPPURATIVE STAGE OF AMOEBOIC HEPATITIS

The extent to which the occurrence of tropical abscesses of the liver can be reduced by the use of large doses of ipecacuanha must evidently depend on the duration of the pre-suppurative stage, in which alone it can be expected to be successful. I have analysed a number of cases of liver abscess to determine this point with the following results. Among twenty liver abscess cases in the European hospital, in 50 per cent fever or hepatitis had been present for over one month before the abscess was found, in 34 per cent more these symptoms had been evident for between two weeks and a month, while in the remaining four cases the time was from nine to thirteen days. Again, out of fifty-three native patients, in 51 per cent a history of over two months' illness was obtained, in 38 per cent one of from one to two months, in 9 per cent from two weeks to a month, and in only one case less than two weeks. Of course, many of the native patients had developed abscesses some time before they came to hospital, but allowing for this, there still remains a good margin of time, in the vast majority, during which the preventative ipecacuanha treatment might have been carried out, with great saving of life and prolonged suffering.

THE TYPE OF THE LEUCOCYTOSIS IN AMOEBOIC HEPATITIS

In the paper already referred to I pointed out that the leucocytosis in amoebic abscess is somewhat peculiar in that the proportion of the polynuclears is usually comparatively slightly, if at all, increased, as it is in ordinary suppurative conditions. A reference to the table will show that a similar type is present as a general rule in the pre-suppurative stages of amoebic hepatitis, and this is a point in favour of the view that these cases are also secondary to an amoebic dysentery, usually of a latent nature. Thus, out of thirteen cases in which the differential leucocyte count was done, in none were as many as 90 per cent of polynuclears present, while in only three were over 80 per cent found. I have

several times found this type a point of diagnostic value in favour of this affection rather than that of some other suppurative or acute inflammatory condition.

THE IMPORTANCE OF ALWAYS TRYING THE IPECACUANHA TREATMENT BEFORE OPERATING

Another striking point in this series is the fact that in no less than one-third of them an unsuccessful exploratory operation was undertaken before the disease was rapidly cured by the ipecacuanha treatment; this indeed was done in several of them at my own suggestion, before I had fully realized how often a marked leucocytosis is present in the readily curable early pre-suppurative stage of amoebic hepatitis. In view of the results of that treatment now brought forward I am strongly of the opinion that all cases of this disease should be treated with large and repeated doses of ipecacuanha, whenever there is any doubt remaining as to whether suppuration has already taken place or not, before any exploration of the liver is carried out, for this rule will certainly prevent some unnecessary surgical measures. Moreover, repeated puncturing of the liver with large aspirating cannulas is by no means without danger, as shown by the number of recorded, and still more of unrecorded, cases of fatal haemorrhage following them, while it is especially in these cases of very acute congestion of the organ without actual suppuration that such deplorable deaths have occurred.

THE PATHOLOGY OF THE PRE-SUPPURATIVE STAGE OF AMOEBOIC HEPATITIS

The explanation of the series of cases just described remains to be considered, and I can best make it clear by beginning with the most straightforward cases and proceeding to the less definite ones, much in the same manner as that by which my present views have gradually become evolved as fresh facts accumulated.

The very favourable position for the study of liver abscess in the tropics which I have long enjoyed, enables me to record that in 1902 I had found living amoebae in 35 consecutive cases of liver abscess in which scrapings of the wall were examined within less than twelve days of the cavity being opened, while the great majority of them were otherwise sterile when first incised. Further, I showed that, when both the clinical history and post-mortem records of cases were available, dysentery had been noted in 90 per cent of the cases, always, in my experience, of the amoebic type. In 18 per cent of the cases the clinical history of dysentery was negative, but nevertheless dysenteric ulcers were found in the large bowel after death, the disease having been present in a latent form—a sequence of events which has since then repeatedly come within my knowledge. I therefore hold that the amoeba dysenterica is constantly present in early amoebic abscess of the liver, although it may very occasionally die out in chronic cases, and that the liver affection is secondary to amoebic dysentery, although this may frequently be present in a latent form and give rise to no typical clinical symptoms, owing to the ulcers being limited to the caecum and ascending colon.

Now, if the above statements are well founded, it follows that in the pre-suppurative stages of amoebic hepatitis, in the absence of any clinical history or actual symptoms

of dysentery, there must be a latent form of that disease present giving rise to irritation of the liver on account of these protozoal organisms reaching the organ mainly by the portal circulation, and that if this source of irritation can be removed the hepatitis should subside. Now it is in just those tropical climates where liver abscess and amoebic dysentery occur that ipecacuanha is looked on as a specific in many cases of dysentery, while I have been informed by several medical men with experience of dysentery in countries where amoebic abscess of the liver is not seen, that this drug is useless in the dysenteries of bacterial origin which they there had to deal with. Personally I look on ipecacuanha as invaluable in the treatment of amoebic dysentery, in fact as a specific against that disease, and in Lower Bengal, where amoebic liver abscess is so common, I regard this drug as second only in importance to quinine itself. If this is so, it is easy to understand how large doses of ipecacuanha (not less than 20 to 40 grains once or twice a day, some twenty minutes after a dose of tincture of opium) may rapidly abort an early pre-suppurative amoebic hepatitis by curing the latent amoebic dysentery that produces it, although I find no recommendation of the drug in some of the standard works on tropical medicine in acute hepatitis, except when symptoms of dysentery are actually present. The cases narrated are, I venture to think, sufficiently striking to warrant the general extension of the ipecacuanha treatment as a routine method in cases of hepatitis in countries where amoebic abscess of the liver occurs, in the absence of actual history or symptoms of dysentery, and that this treatment should always be given a trial before operative measures are undertaken in all cases in which any doubt remains as to whether actual suppuration has yet occurred.

Lastly, we also know that amoebic abscess of the liver may arise sometimes in a most insidious manner, there being no very definite indication of hepatitis for a long time in spite of persistent fever. In such cases, we may also have a latent amoebic dysentery as the exciting cause of the chronic fever, so that it is but one step further to treat these also with large doses of ipecacuanha, as soon as the nature of the case can be determined, for I have shown that they may often, at least, be suspected from the presence of the type of leucocytosis already mentioned. The rapid cessation of the previously persistent intermittent fever, without symptoms of hepatitis, under such treatment in some of the cases narrated, is the best evidence of the correctness of this argument. I am sanguine enough to hope that when these methods of early diagnosis and prompt ipecacuanha treatment of the pre-suppurative stages of amoebic hepatitis become generally known and practised, much will be done to lessen the occurrence of tropical abscess of the liver, with its very high mortality and prolonged suffering, especially in the case of Europeans, who come early under observation for the fever which so constantly precedes, often for several weeks, actual breaking down of the liver substance.

METHODS OF ADMINISTERING IPECACUANHA AND EMETINE

The foregoing results were all obtained by the oral administration of ipecacuanha before I discovered the great advantages over that drug of hypodermic injections of emetine hydrochloride. Since that time emetine has been used with even greater success in amoebic hepatitis, both in cutting it short in the pre-suppurative stage and in

causing encystment and drying up of an already formed liver abscess after the greater part of the pus has been removed by one or more aspirations as recorded in my book on Dysenteries. The rapidity with which an acute amoebic hepatitis will subside, and the profuse expectoration of pus from a liver abscess opening through the lungs will dry up are, indeed, among the most striking manifestations of the specific action of soluble emetine salts. I have also obtained evidence that an already formed small liver abscess may encyst under emetine hypodermically, as one such patient died of a totally different disease some time after the treatment, and an encysted half-eascerated abscess was found after death which was free from both amoeba and bacteria. It commonly requires a longer course of emetine to subdue completely an amoebic hepatitis than to cause dysenteric symptoms to disappear, and a difficulty arises in deciding whether suppuration has already taken place, requiring aspiration or not. Here I have found the total leucocyte count of the greatest value, for if an originally present leucocytosis subsides under emetine it is nearly certain that no pus has formed, or at least that it is present in so small a quantity as readily to undergo encystment without surgical interference. On the other hand, if the leucocytosis persists or increases after a course of eight or more emetine injections it is nearly certain that pus is present and must be sought for with the needle, and removed by aspiration, if in a position where that operation can be safely performed, a cutting operation being seldom required except in some small epigastric abscesses.

In amoebic hepatitis emetine should usually be given hypodermically once a day in 1-grain doses, but in very acute cases, and in patients of heavy weight, such as 12 stones or over, I have sometimes found it advisable to give 1 grain morning and evening for the first two or three days. The toxic effects of emetine must be borne in mind if over 8 grains have to be administered, although as a rule a considerably larger quantity can be given without ill effect. The drug may even produce diarrhoea, and much more rarely some muscular paralysis, especially of the neck muscles. I have found that after from 4 to 8 grains of emetine hydrochloride have been given hypodermically, large doses of ipecacuanha can be administered orally without as a rule sickness being produced, although if given before the emetine vomiting would certainly result. I therefore commonly continue with ipecacuanha after about 8 grains of emetine have been injected in one of the following ways: If the patient can easily take a number of pills, 30 grains of ipecacuanha may be well mixed with 10 grains of tannic acid, which materially helps to prevent sickness, and made up into 5-grain pills, and coated with salol, or the same quantity of the drugs may be dispensed with a drachm of mucilage in an ounce of water. Either prescription may be taken last thing at night after undressing and getting into bed three hours after a comparatively light evening meal, when the patient's sleep will, as a rule, not be disturbed by the drug. I usually give only 20 grains of ipecacuanha, and if retained, increase to 25 the second night, and 30 on the third and subsequent evenings, and continue for at least a week. By this means any amoebae remaining in the bowel may often be destroyed and the danger of relapse of both dysentery and hepatitis materially lessened. I often also use this plan in amoebic dysentery in preference to the extremely irritating bismuth iodine emetine.

Sufficient time has now elapsed to enable the effect of systematic treatment of amoebic hepatitis in its early stages with full doses of ipecacuanha and emetine in reducing the

prevalence of tropical liver abscess to be judged. My results have been fully confirmed, especially by Dudley in the Philippines, and my methods of diagnosis by the blood count and my plan of treatment have been widely adopted. In Calcutta, where I have been able to watch the results in the large hospitals it may be said at once that liver abscess has become a rare disease in Europeans who come early under treatment, and for several years in succession no death has occurred from this cause in the large European General Hospital, while the steady reduction in the number of cases can be seen from the figures in the following table. In the Medical College Hospital, the great majority of the patients in which are Indians, the disease is still only too frequently met with, but the Surgical Registrar informs me there has been a great reduction both in the number of admissions and in the death-rate during the last decade, although unfortunately the records are too incomplete to enable him to supply me with accurate figures. The published records of the British Army in India, however, furnish conclusive evidence on this point, as will be seen from a glance at the accompanying table, which gives the total cases and deaths, and the rates per mille for a number of years.

TABLE XXVI.—BRITISH ARMY IN INDIA

Year.	Admissions.	Per mille.	Deaths.	Per mille.	Case mortality.
1894–1903	157·5	..	92·5
1904	185	2·6	97	1·36	52·4
1905	153	2·1	84	1·18	54·9
1906	183	2·6	107	1·52	58·3
1904–1906	174	2·4	96	1·35	55·2
1907	165	2·4	70	1·01	42·2
1908	115	1·7	55	.80	47·8
1909	100	1·4	34	.48	34·0
1910	75	1·0	35	.48	46·7
1911	71	1·0	33	.46	46·2
1912	47	.7	23	.32	48·0
1913	36	.5	11	.20	38·9
1914	29	.5	9	.20	31·0
1915	23	.5	9	.20	39·1
1916	42	.7	13	.21	30·9
1913–1916	32·5	.55	11	.20	35·0

The figures require little comment as they speak for themselves. It was in 1907 that I published my most important paper on the value of ipecacuanha in preventing the development of liver abscess, and the extraordinary reduction in the number of cases and deaths in the British Army dated from that year, while the earlier figures show no tendency to decline in the previous few years, but rather the reverse. Liver abscess was indeed at that time only second to typhoid as a cause of death in the British Army in India, while the rates per mille of the last four years of which the returns are available show a reduction from the average rates for the three years before my paper was published in the case of admissions from 2·4 to .55, nearly a five-fold decrease, and the death-rate fell from 1·35 to .20 per mille, or almost a seven-fold reduction.

The Army sanitary authorities were at first inclined to attribute the decrease in the liver abscess cases to a decline in the number of admissions returned under the very elastic heading "alcoholism," but an examination of the figures for a decade before 1907 also showed a great decline in the "alcoholism" cases with no decrease, but rather an increase in the liver abscesses; and in the Report of the Sanitary Commissioner with the Government of India for 1913 it was recorded that "The most marked characteristic in connexion with this year's reports on dysenteries has been the success following the use of hydrochloride of emetine administered hypodermically in the amoebic type of the disease, and the remarkable reduction in the number of hepatic abscess cases." The dysentery returns include both amoebic and bacillary forms, and I find the admission rates per mille for the years 1904-1906 averaged 13.7, and for 1913-16 averaged 6.35, or a reduction to about one-half, which will not account for the five-fold reduction in the admission rate for liver abscess. The decline in the case mortality of liver abscess from 55.2 per cent for 1904-1906 to 35.0 per cent for 1913-16 is also satisfactory, and probably due to the use of emetine and the more common employment of my plan of aspiration combined with ipecacuanha orally or emetine hypodermically.

These results fully justify my assertion of over a decade ago that amoebic abscess of the liver is nearly always an easily preventable condition, and that any medical man in whose hands pre-suppurative amoebic hepatitis is allowed to develop into the much more serious suppurative stage should seriously question himself as to how far his treatment has been at fault.

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IX. LOW FEVER—CHRONIC FEVER WITH JOINT AFFECTION —BACILLUS COLI COMMUNIS FEVERS

THERE remain to be described certain less common fevers of long duration which I have met with in my investigations in India. In the first two editions of this work I discussed at some length the series of long fevers among the 1350 consecutive febrile cases I studied in the European General Hospital, Calcutta, which I was not able with certainty to place in the foregoing well-recognized classes of fever, frequently on account of incompleteness of the records, and concluded that they nearly all belonged either to the enteric or kala-azar groups, while I could find no clear indications of any new undifferentiated fevers among them with the exception of the "**low fever**" described below. In the second edition I described an important group of fevers due to the bacillus coli communis, occurring especially in the puerperal state or after genito-urinary operations, and also a rare form of very chronic fever with extensive involvement of the joints due to a minute coccus I cultivated from the blood. The following are brief descriptions of these forms of prolonged fever.

LOW FEVER OF EUROPEAN IMMIGRANTS

In addition to the low continued and intermittent fever occurring in chronic kala-azar cases usually among Indian-born subjects, there is a low intermittent form attacking quite a different class, namely European immigrants, who have commonly resided several years without a break in the trying damp heat of Lower Bengal or Assam. It is seldom met with in hospitals, although not a very rare disease in consulting work on account of its long duration. The essential feature of the affection is a rise of temperature to between 99° and 100°, or occasionally to 101°, especially if the patient goes out in the sun or takes any unusual exercise. The rise always takes place with great regularity in the middle of the day or early afternoon (when the atmospherical temperature has reached about the daily maximum) and declines again in the evening, being usually normal in the early morning. Accompanying this rise there is a feeling of lassitude and disinclination to work, the patient feeling miserable and depressed out of all proportion to the degree of pyrexia; this leads to the temperature being taken and its slight elevation detected. It usually begins in the hot weather, but in some cases it continues through the following cold season, being of an extremely persistent character, and causing much nervous depression. Usually there are no physical signs or symptoms of derangement

of any special organ, although in very long cases some enlargement of the spleen may ultimately develop. The blood nearly always shows a reduction of the leucocytes, from 2000 to 5000 per cubic millimetre being found, while the proportion of lymphocytes is increased to about 40 per cent at the expense of a reduction of the polynuclears to about 50 per cent or under, but usually without any marked increase of the large mononuclears.

As far as I know, this affection only occurs in the damp hot provinces of India, such as Bengal, Assam and Madras, while perhaps the most remarkable feature about it is the fact that, at any rate in its earlier and less intractable forms, a change to a more favourable climate produces an immediate cessation of the pyrexia. Crombie stated that a sea voyage had this effect, the cool breezes and lower air temperature apparently having a beneficial effect. In my experience a change to a dry soil is of the greatest benefit, for I have repeatedly found that a trip to some place on a dry laterite soil, even with a higher air temperature than the part which has been left, caused a sudden and absolute disappearance of the pyrexia as long as the patient resided there, although as a rule it recurs very soon after his return to a damp alluvial spot. A change to England is often necessary in chronic cases to break the fever, but unfortunately the fever may occasionally recur on return to Lower Bengal, even after long leave to Europe. This cessation of the fever in a dry climate in the less firmly established cases is the most characteristic feature of the disease, and one which will usually differentiate it from organic diseases with chronic intermittent fever, which it is most essential to exclude, such as early phthisis or other tubercular disease, and the insidious form of amoebic hepatitis leading to liver abscess. Thus, I have twice seen phthisis ensue on this low form of fever, once after it had persisted for over a year, in which it was probably a terminal infection similar to that in the closely allied kala-azar. The lungs therefore should be most carefully watched. Except for this complication, these cases usually in the end completely recover, although only after prolonged trouble.

The occurrence of this disease among European immigrants, who have usually resided continuously for several years in an enervating hot damp climate, together with its immediate disappearance, in early cases, on a change to a dryer or cooler place, and the invariable rise of the temperature during the hottest part of the day only, all suggest an enfeeblement of the heat-regulating mechanism by prolonged strain as the essential cause of the excessive diurnal variation of the body temperature which occurs. On the other hand, the resemblance of the pyrexial curve to the more chronic forms of kala-azar makes it possible that the disease may be due to some undiscovered protozoal parasite. The common decrease of the polynuclear leucocytes may be only a sign of impaired general health, but it also suggests the possibility of a leucocytozoan parasite, similar to those which A. Bentley first found in dogs in Assam, but I have failed to detect any such organism in the blood of my low fever cases. In the Philippine Islands, again, a fever somewhat resembling kala-azar, but without the Leishman-Donovan parasites, has been met with by Wherry and Woolley.

**CHRONIC FEVER WITH JOINT COMPLICATIONS CAUSED BY A
MINUTE COCCUS**

A very intractable but rare fever met with in Calcutta is characterized by irregular and persistent temperature, accompanied by pains and swelling of the joints which are often acutely tender but without much redness or heat. The duration varies from several months up to three or more years, with remissions and exacerbations. The leucocytes are increased in numbers to the extent of a well-marked leucocytosis with only a slight increase in the proportions of the polynuclears. The heart is not involved, with the exception of haemic murmurs in the more anaemic patients, the red corpuscles being reduced to a moderate extent. The serum reaction to Malta fever is negative even in 1 in 10 dilutions while the patients do not present the appearance or complications of that disease, profuse sweats and orchitis not having been observed in any of them. I have long suspected that some form of coccus might be the cause of the fever, and have now been able both to verify this surmise and to cure by vaccine treatment the following very chronic and severe case.

Fever with Swelling of the Joints of Three Years' Duration ; in which a Minute Coccus was grown from the Blood and the Patient cured by a Vaccine made from it.—A European girl, aged seven years, admitted on July 15, 1907, with a history of having suffered from repeated attacks of fever, accompanied by swelling of various joints, for the past three years. She was very emaciated, the elbows, wrists, knees and ankles were swollen and painful, although not acutely inflamed. The internal organs were healthy, the spleen not being enlarged, and there was no affection of the heart. While in hospital she continued to suffer from fever of an irregular intermittent type, frequently rising to 103° F., sometimes with rigors. In August the fever assumed a high remittent type from 100° to 105°, and twice reached 106°. Sodium salicylate did no good, and antistreptococcus serum was also injected without benefit. In October and November the fever declined again to an intermittent type, but with frequent rises to from 103° to 105°. At the beginning of December Dr. J. G. Murray, I.M.S., under whose care she was, kindly gave her an anaesthetic to enable me to puncture the swollen elbow-joint and take some blood from a vein for culture purposes. No fluid could be found in the joint, the fibrous tissues around it were much thickened. From the venous blood, diluted in a flask of broth, a pure culture was obtained in one day of a minute coccus, which grew on agar in fine transparent droplets, resembling that of a streptococcus, although it proved microscopically to be a minute staphylococcus. It was a very delicate organism, and in spite of frequent transfers it died out before the recently described differential fermentation tests could be carried out, although not before a vaccine had been made. A blood count made at the same time showed 4,790,000 red corpuscles, 26,000 white, with a differential count of 62 per cent polynuclears, 36 per cent lymphocytes, and 2 per cent large mononuclears. She was injected with the vaccine on December 15, when the temperature was of an intermittent type, and received four doses in the course of the next two months. During this time the temperature kept at a much lower level, seldom rising over 100° F., and from the end of March it only occasionally rose to 100°. The joint swellings and pains decreased

with the fall of temperature, and the child has now been completely free from fever for nearly two years. She learnt to walk and run, and became very well nourished, putting on many pounds in weight. No trace of her long illness remains except slight limitation of the movements of the most affected elbow-joint, and the leucocytosis has also disappeared. This case is one of the most remarkable recoveries I have ever seen. Dr. Murray had no doubt whatever that it was due to the vaccine. The micrococcus was certainly not that of Malta fever, but its exact classification remains unsettled. There was no reaction to Malta fever at any time.

A very similar case in a native boy is now under observation, and has improved considerably under treatment by a vaccine made with a coccus grown from his venous blood.

FEVERS DUE TO GENITO-URINARY AND OTHER INFECTIONS WITH THE BACILLUS COLI

Many cases of severe fever accompanying bacillus coli infections, most commonly in the genito-urinary tract, have been recorded in the last few years in Europe and America. Recently they have also been recognized in India, and observations in Calcutta during the last two years have shown them to be a not infrequent cause of obscure pyrexia, the true nature of which is very liable to be overlooked. In India as in Europe the disease is far more common in females than males; this is readily explained if infection be proved to occur through the urethra, which is much shorter in women. In a paper (*Indian Medical Gazette*, November 1909, Supplement) I tabulated 17 cases of genito-urinary bacillus coli infections in the puerperal state and 8 more following gynaecological operations, 5 being for suppurative salpingitis; thus the disease is evidently quite common in the tropics. I am indebted to Lieut.-Colonel C. M. R. Green, I.M.S., for opportunities of research on these patients. In addition I have met with several exceedingly acute general bacillus coli infections of great interest which were not recognized during life. The genito-urinary list of cases presented the following features.

Type of the Fever.—The most marked character of the fever is the irregularity of the temperature curve and the frequency of the occurrence of severe rigors with rapid rises to 104° or 105° F., sometimes more than once in the twenty-four hours. The cases may thus closely simulate serious septic infection due to streptococci, and when present in the puerperal condition give rise to great alarm, although they are usually not very serious if recognized and treated efficiently. The frequent occurrence of well-marked leucocytosis in bacillus coli infections adds still further to the difficulty of diagnosis, as it can usually only be made by a bacteriological examination of the urine. In other cases the rise of temperature is less sudden, taking several days to reach the maximum and more closely resembling a typhoid chart. In one patient whose blood I was asked to examine for typhoid the temperature had risen slowly, but subsequently showed rapid fluctuations, which made me suspect a bacillus coli infection; Widal's test was negative, and on examining the urine it was swarming with bacillus coli. In another case rapid fluctuations of the fever with rigors occurred early after childbirth, but they became more typhoid-like and bacillus coli was found in the urine; the fever eventually yielded quickly to coli vaccine. There

is a tendency for the fever in these cases to subside spontaneously, especially in the slighter infections.

Characters of the Urine.—Except in some long-standing cases, often with little fever, there are usually no symptoms referable to the urinary system in these cases. Unless, therefore, the condition is suspected and the urine examined, the cause of the fever is likely to be overlooked. The urine is nearly always acid, there is no pain on passing it, and often no undue frequency of micturition. It may even be quite clear when the bacilli are few in numbers, but more frequently it is slightly opalescent, which should lead to its being microscopically examined. In such cases a drop of the urine under an ordinary high-power lens will show numerous active rod-shaped bacteria moving in all directions similar to the condition seen in typhoid bacilluria. Sometimes many of the bacteria will be clumped and only a few active. If the urine has been obtained in a sterile test-tube, a pure culture of the coli bacillus will readily be obtained from it. In a few cases the organism is only found on culture, but the fever may be high in such cases. In the great majority of the urines there was no obvious deposit, beyond a little mucus on standing. In some there were no pus cells even on centrifugalization, although occasionally they may be numerous under these conditions. The importance of microscopical examinations of the urine in these cases is obvious, for in the early stage the treatment is generally very satisfactory, although it becomes much more difficult if they are allowed to become chronic.

The puerperal cases are very common in Calcutta, over 20 such cases having been met with in a single year in the Eden Hospital for women. In all but 6 of these the coli bacillus was readily found by microscopical examination of the urine and in 5 of these by culture only. In 1 it was isolated from the uterine discharge. In 5 cases rupture of the perineum requiring suture was recorded, in 3 more, tears of the vaginal wall, these affording opportunities of entrance to the coli bacilli. The time of onset was commonly two to four days after delivery. The infections following gynaecological operations were mostly after removal of suppurating tubes, namely, 5 out of the 8 cases. In 2 there was a recto-vaginal fistula.

In addition to the above puerperal and gynaecological cases, I have met with several other genito-urinary bacillus coli infections in both men and women in India, giving rise to fever of a somewhat obscure nature, thus it is by no means a rare disease.

Several very acute general bacillus coli infections have also been recognized in the post-mortem room after death from an acute febrile attack. The patients were usually admitted in an unconscious and almost moribund condition, some of them having been suspected to be plague. In two of these a thickened congested appearance of the large intestine, resembling early bacillary dysentery, was found, but a pure culture of bacillus coli was obtained from the spleen. Small haemorrhagic ulcers were also present in the stomach in one, resembling plague, and it was only on making cultures from the spleen that the cause of the septicaemic process was recognized. Cases of multiple small suppurating points in the liver and spleen respectively, due to coli bacilli, have also been met with, infection of the bladder being present as well in one renal case. The other patient had acute hepatitis in hospital with 91 per cent of polynuclear leucocytes, and the

gall-bladder as well as the portal veins contained coli bacilli. These cases have not yet been recognized during life.

Treatment.—The importance of being on the look-out for fevers due to bacillus coli infection is that they readily yield to vaccines, often to a stock one, but sometimes vaccines require to be made from the patient's own bacillus.

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X. OROYA FEVER OF PERU

History.—This disease has long been known in Peru and is believed to have caused many deaths in Pizarro's army in the sixteenth century, while it certainly produced a high mortality during the construction of the central railway from Lima to Oroya in 1870. In 1885 Daniel Carron, a medical student of Lima, inoculated himself from the warty-like lesions of *verruca peruviana* and died of high fever thought to have been Oroya fever, and for long these two diseases were believed to be closely allied, although according to Strong there is no accurate record of Carron's fatal illness, which may have been typhoid. In 1901 Barton described a bacillus-like body in the red corpuscles of Oroya fever, while others considered the disease to be paratyphoid. From 1913 to 1915 Richard P. Strong, Tyzzer and Sellards published a series of papers on their investigations in Peru in which they produced strong evidence that Oroya fever is quite distinct from *verruca peruviana*, the latter being a purely local inoculable infection, the virus of which is unknown, but produces characteristic lesions when inoculated into the testicles of rabbits, while Oroya fever is due to the organism first described by Barton, but cannot be conveyed to animals by injection of the blood of infected persons. The following brief description of the disease is based on the work of Strong and his colleagues.

Description of Oroya Fever.—The disease is not limited to the Oroya Valley, but probably extends to many other parts of the Peruvian Andes. It is most prevalent from January to April, especially towards the close of the warm rainy season. The incubation period is said to be about twenty days. The fever in severe forms is irregular and accompanied by a rapid and often fatal pernicious anaemia, which may terminate life within three or four weeks, while the red corpuscles may fall to 1,000,000. The fever is usually irregularly remittent or intermittent, and in recovering cases improvement begins after twenty-five to thirty days. The mortality is usually from 30 to 40 per cent. The spleen is frequently enlarged, and sometimes also the liver, while the glands are almost always more or less increased in size.

The Blood shows normoblasts and megaloblasts, and leucocytosis is almost always present, 20,000 being commonly found without any material change in the normal proportions. Myelocytes may also be present. The haemoglobin may fall to 15 per cent. Strong describes the parasite as follows: "Bartonia bacilliformis. Gen. et sp. nov. Parasites consisting of rounded or oval forms or of slender straight, curved, or bent rods occurring either singly or in groups, but characteristically in chains of several segmenting

organisms, sometimes swollen at one or both ends and frequently beaded. Reproduction by binary division. Endowed with independent motility, moving in the direction of the long diameter, living within the red blood corpuscles of man and producing a grave form of anaemia known in Peru as Oroya fever. Stained preparations suggest differentiation of cytoplasm and nuclear material."

The Pathological lesions found are anaemia with small haemorrhages and oedema or congestion of the lungs, enlargement of the spleen, often with infarcts, enlargement of the liver with areas of necrosis due to toxic degeneration and fatty and hyaline changes in the cells; mesenteric and lymphatic glands enlarged and congested, while the large intestine occasionally showed superficial ulceration. The bone marrow, liver and spleen show phagocytosis of damaged cells, while in the spleen and lymph glands are seen large swollen endothelial cells often containing many round or rod-shaped parasites similar to those found in the red corpuscles in the blood.

C. H. T. Townsend, Entomologist to the Peruvian Government, disagrees with Strong's view, and maintains the former one that *verruca peruviana* is but a mild local lesion of the same disease which when severe and acute produces Oroya fever. He has brought forward strong evidence that *verruca peruviana* infection is conveyed by the bites of phlebotomii, and produced lesions in a dog through these insects. The infection takes place at night when sleeping within an endemic area. There appears to be still much to be learnt regarding these diseases.

Treatment.—No drugs are known to have any curative value in this disease.

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XI. TRENCH FEVER

A FEVER which has caused much sickness more especially on the Western front in the British Army has become known by the not very appropriate name of "trench fever." The most important of the early work on the subject was that of McNee, Renshaw and Brunt, who described two types of the disease, and demonstrated that the red corpuscles of patients contained the infective agent. Lice were soon suspected to be the carriers of the infection, and satisfactory proof of their doing so has recently been forthcoming. In addition to France and Flanders, cases have been reported from Salonica and Mesopotamia.

Etiology.—In their paper of April 1916 McNee and his colleagues stated that all their cases had occurred either in men from the trenches or in those of the Medical Corps in attendance on them. A little later Muir and others pointed out that men who had not been in the trenches were also attacked, while two workers have recorded cases in England in military camps among men who had not been abroad, so the term "trench fever" is largely a misnomer. The high incidence of the disease is shown by Muir's having found that 44 per cent of the admissions to his field ambulances were for this disease, while Grieveson had 25 per cent of his total admissions, and as many as 60 per cent from certain platoons within a single month, clearly indicating the serious loss of man-power due to this disease. Muir has recorded figures showing great increases of the numbers of cases during hard work in the trenches, and equally well-marked decreases during comparative rest after withdrawal from the trenches to camps in the rear, while he also noted an increase during hard training in the camps, indicating that fatigue predisposed greatly to the infection. Grieveson has pointed out the special incidence of the disease in certain platoons as shown by the fact that in a certain line one half had six and a half times as many cases as the other half, and he met with numerous instances in which fourteen days after the occurrence of a case in one platoon two or three more of his co-sleepers were attacked, and he therefore strongly supported the lice-infection theory.

As there was no mortality from the fever, McNee and Renshaw, after failing to infect animals, carried out a series of experiments on volunteers by injecting whole blood, plasma and serum both filtered and unfiltered, and red corpuscles freed from serum by washing, and established the important fact that both whole blood and the washed corpuscles conveyed the infection, but that plasma or serum, whether filtered or not, was harmless. They therefore concluded that the infective agent was in the blood corpuscles, although they could not demonstrate it microscopically. Another important step was taken when

Davies and Weldon reported that one of them developed a typical attack of trench fever twelve days after allowing himself to be bitten by lice which has just previously been fed on two patients in the acute stage of the fever. Early in 1918 a Committee, with Sir David Bruce as Chairman, was appointed by Sir Alfred Keogh, and reported successful experiments carried out by Byam in the Hampstead Military Hospital. In the first test two volunteers were bitten by at least 500 laboratory-bred lice previously fed on trench fever patients in all stages of the disease from France, but with entirely negative results. The patients had been careful not to scratch themselves, which precluded the contaminative mode of infection, so two more volunteers were experimented with in the following manner : A small area of their skin, 1 inch square, was lightly scarified, and in one patient dried excreta from fed lice were rubbed in, and in the other eleven trench-fever-fed lice were crushed on the scarified area. Both contracted typical trench fever after eight and ten days' incubation respectively, and the experiment was repeated with similar success. The mode of infection has thus been cleared up, as scratching induced by the bites of lice serves to rub the infective agent into the wound inflicted by their bites. The experiments also showed that when a patient gets fever any lice on him will quickly desert him to go to one without fever, thus tending to spread the disease among co-sleepers as Grieveson noted.

Prophylaxis thus consists in the destruction of lice, which is now being carried out as far as possible. Methods of dealing with these pests will be found in the section on typhus fever, page 143.

CLINICAL DESCRIPTION

The Onset is usually sudden, with headache and pain in the back of the eyes, dizziness and pains in the lower extremities, especially the shins, and in the back. The **bowels** are often constipated, and the tongue is furred and Grieveson describes as very characteristic a red margin about one-sixth of an inch in width with thick yellow fur over the rest of the organ. The **pulse** rate is only slightly raised to about 100 with a temperature of 103° to 104° F. The **spleen** is rarely sufficiently enlarged to be palpable, but its dulness has been reported to be increased.

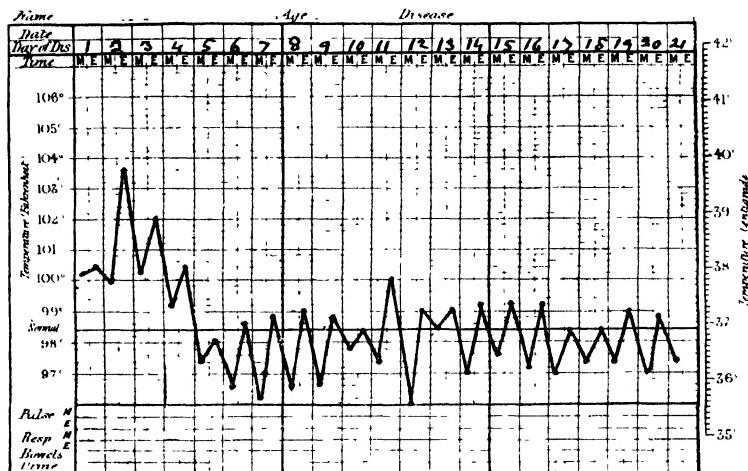
The Fever runs a very variable course, and cases have been subdivided by Mcnee into an acute class of short cases with fever of about six to eight days' duration, with a remission about the third day, and often followed by a single very short rise to 100° to 101° F. within about four days of the first fall to normal (see Chart 37); and a second rarer relapsing form with a shorter initial fever, several relapses of only about thirty-six hours' duration with intervals of about four days, and recurrence of the headache, pains and other symptoms with each recurrence (see Chart 38). The second and third relapses are usually as severe as the first fever, after which they become less so, although the pains in the shins remain troublesome. Byam and others describe a still more chronic form in which attacks continue to occur at long intervals, so that the total duration may extend to from three to eighteen months, the average being about six months. In such cases are encountered irritability of the heart, with shortness of breath on slight exertion, tachy-

TRENCH FEVER

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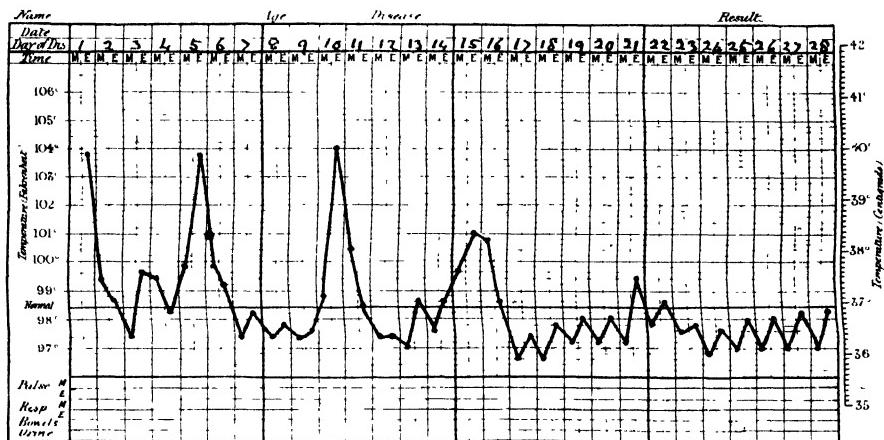
cardiac and nervous symptoms, especially hyperalgesia and deep muscular tenderness, most extensive during the febrile relapses. In this form permanent disability from

CHART 37



Trench fever. Short type (McNee).

CHART 38



Trench fever. Relapsing type (McNee).

service results. Much weight is lost in all the relapsing forms. Catarrhal symptoms are absent.

The Blood showed the following average figures in eleven counts by McNee: haemoglobin, 84 per cent; red corpuscles, 5,290,000; and white corpuscles, 8883, the latter having varied between 5200 and 18,200, but only exceeded 10,000 in three cases. The differential counts only showed a slight relative increase of the large and small lymphocytes and low hyaline cells.

The Mortality is nil, and in the short acute type convalescence is fairly rapid, but is much slower in the relapsing form.

Differential Diagnosis.—In the early stages of the more acute cases typhoid or paratyphoid may be suspected, but very numerous cultures from the blood always gave negative results. Cases were at first frequently returned under the elastic head of influenza, but the absence of all catarrhal symptoms and lung complications excludes that disease. Dengue is much more closely simulated, but rash is entirely absent, leucopaenia is not present, while the disease continued during the winter months in France, when dengue subsides even in semi-tropical climates. Relapsing fever may be excluded because of the absence of the spirochaete from the blood and of the presence of a marked polynuclear leucocytosis and malaria by the absence of the parasites of that disease.

Treatment.—This is mainly symptomatic. Rest and attention to the bowels are first indicated. Phenacetin and sodium salicylate help to relieve the pains. Muir states that in cases seen very early two powders, each consisting of morphine acetate, gr. $\frac{1}{4}$, caffeine citrate, gr. 1, and phenacetin, gr. 8, one given on getting the patient to bed, and the other two hours later, will sometimes cut short the fever. Byam has tried galyl and acriflavine, and recommends the latter in the form of a 1 in 1000 solution in normal saline, of which 200 c.c. should be given intravenously as a single dose, or 0.025 grammes of the drug may be injected daily. He also found that lumbar puncture with the removal of 10 c.c. of fluid gave immediate relief to both the pain and hyperalgesia. Locally, twenty drops of a solution of 10 grains of menthol in 2 drachms of Oleum gaultheriae, covered with protective tissue and cotton wool, gave prompt relief. Quinine, iron and arsenic are useful as tonics during convalescence.

NOTE.—In a subsequent paper Byam states that the early good opinion of acriflavine has not been maintained. He has discontinued its use.

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B. Fevers of Short Duration

XII. MALARIAL FEVERS

THE INCIDENCE OF DIFFERENT FORMS OF MALARIA IN VARIOUS COUNTRIES

MALARIA is the most widely distributed disease of tropical and sub-tropical countries, but varies greatly in the relative prevalence of the three types of the disease, namely, Malignant Tertian due to the *Plasmodium falciparum*, Benign Tertian due to *P. vivax*, and Quartan due to *P. malariae*. The following table gives the distribution of these forms in some different countries collected from recent literature on malaria.

TABLE XXVII.

Country.	Observer.	Cases.	Positive.	M.T.	B.T.	Quartan.	Mixed.	Spleen Index.
Albania	Andruzzi	98·0	2·0	0·3
Macedonia	Abrani	85·0
Jerusalem	Muhlens .	2114	21·0	45·2	41·5	13·3
"	Brunn and Goldberg .	2055	21·5	60·0	16·0	21·0	13·3	59·0
Mesopotamia	Richardson	13·0	87·0
Upper Senegal and Upper Niger	Leger .	859	90·5	36·9	4·1	58·9
Argentina	Barbieri	1·4	62·1	10·5	26·0	..
French Guiana	Leger	28·0	68·0	3·0	..	17·0

The above figures show remarkable variations in the proportions of the three types of malaria in different countries. The high proportion of malignant or sub-tertian malaria due to the *Plasmodium falciparum* in Macedonia and Albania is noteworthy. Armand-Delille noted in the French Army in the Near East that malignant tertian malaria was absent from February to June, while a great rise occurred in October, and that benign tertian cases kept at a low level until the main rise occurred in July and August: very much what I found in Calcutta. In Africa malignant tertian malaria usually greatly predominates, and Macfie on the Gold Coast notes that it is far the most frequent form, although Leger found the quartan form to predominate in Senegal and the Upper Niger.

In Western China Jouveau-Dubreuil noted that 57.9 per cent were malignant tertian, while in Tonkin Mathis and Heymann found the endemic index in numerous children to be only 5.7 per cent. Mathis also states that 12 per cent of the European mortality was from blackwater fever. The United States Southern Medical Association investigated the prevalence of malaria in the south of the United States, and found benign tertian malaria most prevalent in the northern portions and malignant tertian in the southern area.

The Prevalence of Malaria in India.—It is only during the last few years that accurate data regarding the prevalence of different varieties of malaria and their seasonal incidence in different parts of India have begun to accumulate. Previously to the recent more extensive use of the microscope in the diagnosis of fevers in India, our knowledge of the subject was derived solely from clinical impressions, many of which are now known to be entirely erroneous. It will therefore be advisable to set forth such reliable facts as have been recorded as concisely as possible, as they are now sufficiently numerous to afford fairly clear ideas on the distribution of malarial fevers in the most important provinces of India, which will at least serve as a guide to what may be expected in places where the question still awaits investigators.

In order to ascertain the prevalence of malarial fevers in any place, it is necessary for a competent observer to examine the blood of all fever cases which may possibly be malarial for the space of at least one complete year, and to note the different varieties of parasites found in them. Table XXVIII. gives as many such data as I have been able to collect.

Prevalence in Calcutta.—The most complete records are those of Calcutta, where Captain J. W. D. Megaw has systematically examined the fever cases coming for one year to the large Medical College Hospital, most of the patients being natives of India, while I have made similar observations at the European General Hospital for two years. Both the monthly and quarterly figures for each of the three types of malaria are shown in the first part of the table. Taking first my own figures for the European Hospital, out of 200 cases in two years 99 were malignant tertians, 96 being tertians and only 5 quartans. The quarterly distribution shows that more than half the cases occur in the last three months of the year, and one quarter from July to September. In the first half of the year only 20 per cent of the cases occurred, being nearly equally distributed over that period. Thus, the most marked malarial season is during the drying up at the end of the south-west monsoon from October to December. They are next most common during the rainy season, which lasts from the middle of June to early in October, and they are much less prevalent during the dry first half of the year.

Turning next to the different varieties of malaria, we find great differences in their monthly distribution. Thus the **malignant tertians** have a most marked predilection for the last three months of the year, during which 70 per cent of the cases occurred. In the third, or rainy, quarter 23 per cent were met with, while in the whole of the first half of the year only 7 per cent were seen, February and March showing no cases either year. The **benign tertians** also show a maximum prevalence in the last quarter, when rather

over half the cases occur, while over one-fourth were met with in the third quarter. They differ, however, from the malignant tertians in being more uniformly distributed over

TABLE XXVIII.—MONTHLY INCIDENCE OF DIFFERENT FORMS OF MALARIAL FEVER IN INDIA

	Calcutta, two years' cases in Europeans.	January.		February.		March.		1st Quarter.			April.		May.		June.		2nd Quarter.			July.		August.		September.		3rd Quarter.			October.		November.		4th Quarter.			Total.	Percentage.
		Quartan	Benign	Tertian	Malignant	Tertian	Benign	Quartan	Benign	Malignant	Tertian	Quartan	Benign	Malignant	Tertian	Quartan	Benign	Malignant	Tertian	Quartan	Benign	Malignant	Tertian	Quartan	Benign	Malignant	Tertian	Quartan	Benign	Malignant	Tertian						
		.	.	5	5	4	14	5	6	7	18	9	10	10	29	11	17	7	55	96	48·0																
		Quartan	Benign	Tertian	Malignant	Tertian	Benign	Quartan	Benign	Malignant	Tertian	Quartan	Benign	Malignant	Tertian	Quartan	Benign	Malignant	Tertian	Quartan	Benign	Malignant	Tertian	Quartan	Benign	Malignant	Tertian	Quartan	Benign	Malignant	Tertian	49·5					
	Total .	.	9	5	5	19	6	7	9	22	18	17	18	53	30	48	29	107	200																		
	Megaw's one year's Medical College cases, Calcutta.																																				
	Quartan	.	6	6	3	15	1	1	1	3	2	4	..	6	3	4	3	10	34	10																	
	Benign																																				
	Tertian	.	9	9	2	20	5	2	4	11	2	11	18	31	14	20	16	50	112	33																	
	Malignant																																				
	Tertian	.	16	3	5	24	6	5	4	15	7	13	25	45	44	39	26	109	193	57																	
	Total .	.	31	18	10	59	12	8	9	29	11	28	43	82	61	63	45	179	339																		
	Powell's two years' Bombay cases.																																				
	Quartan	.	1	1	2	4	3	9	6	18	2	2	2	6	2	2	1	32	1·4																		
	Benign																																				
	Tertian	.	74	50	69	193	59	72	64	195	132	140	113	385	137	146	108	391	1164	52·6																	
	Malignant																																				
	Tertian	.	77	61	50	188	60	60	72	192	87	82	88	257	130	139	113	382	1019	46																	
	Total .	.	152	112	121	385	122	141	142	405	221	224	203	648	269	285	223	777	2215																		
	Dr. Laura Hope's one year's Pubna cases (Eastern Bengal).																																				
	Quartan	.	123	122	141	386	46	60	85	191	72	64	51	187	19	51	69	169	933	52·3																	
	Benign																																				
	Tertian	.	16	9	20	45	49	27	9	85	16	7	9	32	7	25	23	55	217	12·2																	
	Malignant																																				
	Tertian	.	72	35	29	136	61	28	16	105	19	28	38	85	62	81	78	221	547	30·6																	
	Mixed .	.	4	7	14	25	11	8	8	27	5	2	6	13	3	12	7	22	87	4·9																	
	Total .	.	215	173	205	592	167	123	118	408	112	101	104	317	121	169	177	467	1784																		

the year, so that one-third of the cases occur in the first dry half, and in no month did they disappear. The quartans in my series were very few, and were still more uniformly distributed over the year.

In Megaw's Calcutta Medical College series of 339 cases, over 90 per cent of which

were in natives of India, a very similar distribution of the different varieties is seen, the malignant tertian being the shortest, the benign tertians somewhat more generally distributed. The quartans are of special interest, for here there is much more uniform distribution over the year, even than in the case of the benign tertians. They were rather more prevalent in the last quarter, but the largest number were seen in the first quarter of the year. Adie also notes that quartan malaria is met with at all seasons of the year at Ferozapore in the Punjab. The large proportion of quartans in the Pubna series is striking, while they are also common in Assam.

These differences in the seasonal distribution of the different varieties of malaria do not necessarily indicate that the time of infection in benign tertians and quartans is much more extended than that of malignant tertians. A more likely explanation is the greater tendency of the two milder forms of infection to relapse again and again, and so tend to be more frequently admitted at a remote period from the original infection. This, again, may be due to the much slighter degree of constitutional disturbance in these forms, leading to neglect of treatment or too early cessation of quinine, than in patients subject to the more severe malignant tertian infection. This is borne out by a table given by Megaw showing a larger proportion of patients with the benign infections, who came for treatment after having suffered from fever for a month or more. In my own series I have also observed a greater frequency of relapses in these mild types of malaria.

In **Bombay** the seasonal incidence in a large series of cases in the police hospital has been worked out by Dr. A. Powell for a period of two and a half years. The figures for two complete years are shown in the table, and they present very similar features to those just described. The main point of difference is the larger proportion of cases met with in the first half of the year, especially in the case of malignant tertian infections. This is probably associated with the more uniform temperature in Bonibay than in Calcutta, so that there is no season sufficiently cold as to cause an entire cessation of new infections. In Calcutta I showed some years ago that there is a very marked and rapid decline in the number of intermittent fevers in December coincidently with a fall in the minimum air temperature to 60° F. or below. This no doubt acts by preventing the complete development of the mosquito cycle, for recently Jansco has shown that rapid development of the parasite occurs in *Anopheles claviger* between 24° and 30° C., and a slower one at slightly lower ones. At 16° C. no development takes place, but if the temperature is only lowered to below 16° C. after some development has taken place it proceeded, so that it is conceivable that the infection may be continued by hibernating mosquitoes. In Bombay and Madras such cold weather as this is not met with. It also shows the maximum prevalence in the last quarter of the year, the next greatest being again in the third rainy quarter, while only one-fourth of the cases occurred in the first half of the year.

In Bareilly, in the United Provinces of Agra and Oudh, Major Buchanan, R.A.M.C., found benign tertians to constitute over 90 per cent of the total cases. I also examined all the records of all the fever cases in the Lahore Medical College Hospital, but here unfortunately the kind of malarial parasites found had not been noted. The charts, however, enabled me to classify the majority fairly accurately, and they showed a very similar seasonal distribution of the benign and malignant tertian types to that met with in other

parts of India, only there was an early decrease of cases in December, and a very low incidence from then on through the whole of the first half of the succeeding year. This is quite in accordance with the early, severe and prolonged cold season in this province as distinguished from Calcutta. In Madras I was unable to get complete records.. The cases returned as malarial showed a very similar seasonal distribution to those of Bombay, which has nearly the same temperature conditions as Madras. C. Donovan, in Madras, found malignant tertian parasites most frequently, while quartans were rarest as elsewhere.

Mortality from Malarial Fevers in India.—The vital statistics of the civil population of India show that 90 per cent or more of the deaths are returned as being caused by fevers, and they have often been quoted as an evidence of the enormous mortality from malarial fevers. As a matter of fact they afford no indication whatever as to the real mortality from fevers in general, and still less that of any particular kind, as the deaths are reported by ignorant village headmen or watchmen, who return every kind of illness as "fever." Some general ideas as to the principal causes of death may be obtained from the results of an inquiry into 1000 fatal cases in the very feverish district of Dinajpur in Lower Bengal. All the deaths returned as due to fever in one year in selected areas of the district were investigated by obtaining the history of the illnesses from the relatives of the deceased.

I thus found that one-third of the deaths attributed to fever were due to diseases such as dysentery, tumours, etc., in which fever was not even a marked symptom ; another third were caused by such diseases as pneumonia, bronchitis, phthisis (the last constituting 9 per cent of the total) and typhoid ; while the remaining third were due probably for the most part to malaria and kala-azar. Of the deaths which appeared to be clearly due to malaria no less than three-quarters were in children under 15, and the great majority of them occurred in the four last months of the year, which we have already seen to be the regular maximum malarial season all over India. They formed 15 per cent of the whole. In a further 18 per cent there was evidence of cachexia with marked enlargement of the spleen and prolonged fever, but it was impossible to say how many of them were true malarial cachexia and how many sporadic kala-azar, although the fact that *I found the parasites of the last disease in ten out of thirty spleen punctures and those of malaria in only five cases*, points to the former disease as the cause of many of these deaths. We thus arrive at the conclusion that at any rate in this specially malarial district the deaths really due to malarial fever probably amounted to but from 20 to 25 per cent of the total fever mortality, which is still an appallingly high rate for such a readily curable disease. As the prevention of infection by mosquitoes in village communities in India is an absolute impossibility, for 99 per cent of the population of this district live in separate houses, widely dispersed among rice and jute fields, I advised the distribution of quinine through the agency of the village schoolmasters, who are in a position to reach the children, among whom the vast majority of the deaths occur. This proposal has been extensively adopted in India, and when the contemplated extension of the cinchona plantations to meet the increasing demand for the drug is carried out something will be done to lessen the terrible mortality from malaria among native children in India.

The Endemic Index of Malaria.—An important advance was made when Koch showed

that in very malarious places a considerable percentage of the apparently healthy children showed malarial parasites in their blood, from whom mosquitoes might become infected and in turn convey the disease to Europeans living in houses near native huts. Stephens and Christophers, in the course of three years' labours as Commissioners of the Royal Society in Africa and India, confirmed and greatly extended our knowledge in this direction. They showed that the degree of malaria in any place could be measured by the percentage of healthy children showing malarial parasites in their blood, and termed this figure the "endemic index of malaria." Thus, in Calcutta they examined the blood of a large number of children without finding any malarial parasites and, consequently, recorded the endemic index as 0. At Barrackpur, 15 miles north of Calcutta, 7·7 per cent of the children were infected, and this figure represents the endemic index of that place. On reaching Jalpaiguri, some 300 miles farther north, and contiguous to the district of Dinajpur referred to above, the endemic index rose to 12·7 per cent, and in the notoriously malarial Duars, a tea-planting area at the foot of the Himalayas, rates of from 43 to 72 per cent were met with. In the latter places a particular variety of anopheles (*A. listoni*), which was specially frequently found to be infected with malaria, was common, although it is rarely found in less malarious parts.

This method of testing the relative amount of malaria in a district is of great value, but requires an expert microscopist with a good deal of leisure. By its means the investigators showed that only a few areas of the places they visited were intensely malarial, and that there are still some unknown factors influencing the prevalence of this disease, although the carrying powers of different varieties of anopheles have doubtless a good deal to do with it. They had not time to work out the variations in the endemic index in different seasons of the year, with regard to which more information is still required. That it varies greatly is shown by some observations I made in very malarial tea-gardens in the Nowgong district of Assam, where the endemic index reached the very high figure of 80 per cent in October, at the end of the rains, but was only 30 per cent in the same place early in April at the end of the less malarial cold season.

Stephens and Christophers maintained that new infections of malaria could not arise in Calcutta, because the endemic index was 0, and they had not found the species of anopheles which most readily conveys the infection. This was contrary to all clinical experience, and moreover their examinations of children were made at seasons other than that of the maximum prevalence of malaria in Calcutta. Captain Megaw and myself, therefore, examined the blood of 200 children in November at the height of the malarial season in the suburbs of Calcutta, from which the majority of malarial cases are admitted. Our observations confirmed those of the Commission in showing an absence of infection in the children, except that a low rate of infection was found at one place five miles south of Calcutta and resembling Barrackpur in its situation. Even at Garden Reach, from which many cases of recent malaria are admitted, occurring among European horse-dealers who come from non-malarial parts of Australia, the rate in 30 children was 0, although malaria was, at the time of our observations, so rife among the native police that the great majority of them had been to hospital for fever with malarial parasites in their blood. It is therefore clear that an "endemic index" of 0 even in the malarial season is not proof that there is no malaria in any given place, although a high rate is certainly evidence of a place being

very malarial. Further, Megaw has recorded a number of cases of malaria arising in the heart of the native portion of Calcutta in children who had never been away from the town for a single day. Moreover, S. P. James has stated that malaria is absent from certain places in Assam, because he failed to find malarial parasites in the blood of twenty or so children living there. In my experience such a small number does not give reliable results, for in one instance twenty slides would have given 0 as the endemic index, while thirty cases gave one of 15 per cent. It is clear, then, that this test must be used with caution and malaria must not be declared to be absent because a few healthy children show no parasites in their blood at any particular season of the year.

The Spleen Test for Malaria.—Dempster's spleen test for malaria was first used by him in India in 1845, in an inquiry into the prevalence of malaria along the Delhi canal, twenty children and twenty adults being examined at each place for enlargement of the organ. A much higher spleen rate was found in the more malarious places than in others with less fever. In my Dinajpur and other inquiries I found the spleen rate to increase with the increased death-rate from malarial fevers, while the Malaria Commission also showed that the spleen rate in children rose with the increase of the "endemic index" for malaria, and that too in Lower Bengal, where sporadic kala-azar is very prevalent. The death-rate of the latter disease is so high in children that it is unlikely that any marked proportion of the enlarged spleens found among them can be due to that disease, unless it is present in the epidemic form which recently overran the Assam Valley. The advantage of this test is that it can be very rapidly applied by any medical man, and will ordinarily give all the information necessary as to the prevalence of malaria. Moreover, it can be used for comparing the unhealthiness of neighbouring places or parts of a district at any time of the year, and this is very important, as such inquiries have usually to be carried out in the cold season when malaria is not very prevalent, and the endemic index may be very low, in spite of much malaria in the season of its maximum prevalence.

Ground Water-Levels and Malaria.—In the Dinajpur district I found a close relationship between high ground water-levels throughout the year and both high spleen and malarial death-rates, while low ground water-levels were accompanied by much less prevalence of malaria. The great improvement in health in Algeria, following a lowering of the ground water-level by drainage, shows the great value of this measure, which has also given good results in certain small areas in Lower Bengal.

Rainfall and Malaria.—In an investigation of the great Punjab outbreak of malaria in 1908, which caused an increased death-rate of 300,000 in the last three months of the year, Christophers showed an intimate relationship over a long series of years between flooding due to excessive rainfall and epidemic, or better fulminant, malaria. Gill also studied the question and found fulminant malaria to be most prevalent in subtropical areas where infection is usually absent for a considerable portion of the year, allowing a high degree of susceptibility of the people to develop. In 1909 in connexion with the Mian Mir Malaria Commission I examined the rainfall and fever data for thirty years, and also found an intimate relationship between high rainfall and increased malarial prevalence and that the fairly even distribution of the rain, leaving insufficient intervals for the pools

of water to dry up, increased its effect. As early as 1894 I had demonstrated a very close relationship between a heavy monsoon rainfall and high malarial incidence in Indian regiments in Chota Nagpur. On the contrary, in the parts of Eastern Bengal which are always flooded for some months during the monsoon, a short rainy season with an early and prolonged drying up in the malarial autumn months causes an excess of malaria. By studying such local relationships between meteorological conditions and malarial prevalence it should usually be possible to foresee outbreaks of excessive malaria in good time to take especial steps to deal with them, so far at least as the saving much life by distributing quinine freely among the suffering population is concerned, as was done to a considerable extent in the 1908 Punjab epidemic.

Race Incidence and Acquired Immunity.—The work of Koch, Stephens and Christophers, in the Dutch West Indies and Africa respectively, on the great prevalence of malaria among children and the practical immunity of adults, came as a surprise to workers in India, where malaria is common enough in native adults. The latter observers have, however, shown that in the most malarious parts of India, such as the Duars already mentioned, a very similar, if less extreme degree of infection in children exists, while adult native immunity prevails to some degree, and that Europeans living close to native huts are very liable to infection. A considerable degree of segregation of Europeans exists in most Indian stations, owing to the cantonments for European soldiers and the residences of European officials being situated at a distance from native towns. From one-quarter to half a mile is considered sufficient distance by the Malaria Commission, and should always be enforced. Rest bungalows, etc., should also be placed at a similar distance from native villages. The dosage of native children with quinine in a community was also shown in the Mian Mir experiment to prevent infection of the adults. The immediate treatment of all native servants suffering from malaria is also very advisable for the protection of their European masters.

Predisposing Causes of Malaria.—A severe infection with malarial parasites will doubtless produce fever without the aid of any predisposing causes. Nevertheless, the first attack may appear after removal for some time from the place where the infection was contracted, when some predisposing cause allows the parasites to multiply more rapidly and produce an attack of ague. Again, in a series of admissions for malaria the number of fresh infections is probably smaller than the number of relapses. For these reasons various debilitating causes may often be important factors in exciting an attack of malarial fever. In some places chills produced by a sudden fall of some 30° F. due to heavy rain may cause an increase of malarial admissions, while in another the trying damp heat of a break in the monsoon may have a similar depressing influence. A chill on passing from a hot to a colder climate often has the same effect, as also in moving from the Indian plains to the hills or to Europe. In all these cases a latent malaria is roused into activity, and many cases of the disease may thus arise either in the minimum malarial season in the tropics or after removal from a malarial region, being more common in quartans and benign tertians than in the malignant form. Such relapses are evidence of insufficient treatment and indicate a prolonged course of quinine.

Age and Sex Incidence.—It has already been mentioned that malaria is specially prevalent and fatal among native children. In the case of my European series in Calcutta we have two different classes to deal with, namely, the immigrant class and those born and bred in India, who are nearly all of mixed European and Indian blood, and for the most part live in parts of the town which are also inhabited by natives. The majority of malarial cases among immigrants occur in young adult males because these form such a large proportion of this class. Among the indigenous Indian-bred Europeans nearly half the patients were under the age of 20, while 28 per cent were 15 or less, so that there does not appear to be so marked an incidence among European as among native children as compared with adults. This is probably due to the Europeans being much less exposed to malaria in Calcutta than natives are in the districts, so that Europeans suffer less as children and so do not acquire the same degree of relative immunity when they reach adult life. The sex incidence of the Indian-born Europeans was equal in the case of children of 15 years and under, but over that age there was a marked preponderance of males, namely, 40 males to 24 females. This is partly due to an excess of males of this class in the population, and partly to the men moving about in the districts where they are more exposed to infection than in Calcutta itself. I find no difference in the prevalence of benign and malignant tertian fevers in my European series. Among the immigrant class (which include a few sailors, who had contracted malaria in Mauritius or other ports), nearly one-half had been a year or more in the country, while only one-fifth, including those who reached India with malaria, came to hospital within the first three months of residence in India. One-fourth were attacked in from three to twelve months' residence, so that of those attacked nearly half suffered within one year of coming to India.

THE PARASITES OF MALARIA

Although a considerable proportion of malarial fevers can be correctly diagnosed from the temperature curves, still, even in such cases it is very important, whenever it is possible to do so, to verify the conclusion arrived at by means of a microscopical examination of the blood for the parasites. The absolute certainty thus reached will enable the prolonged course of quinine treatment, which is so essential for the permanent cure of the disease, to be more confidently insisted on. Cases in which any doubt remains clinically as to the presence of malaria most urgently demand such a microscopical test either to confirm or exclude the suspicion of the disease, for nothing has been so detrimental to the progress of our knowledge of fevers in India as the blind treatment as malaria of almost every pyrexial condition occurring without an obvious cause for days, and even weeks, until signs of liver abscess or some other evident cause obtrudes itself. The impossibility of examining the blood in every fever patient under the ordinary conditions of work under high pressure in India has too often led to this valuable method being almost entirely neglected, but if the majority of the cases can be diagnosed clinically by the methods described in this work, then it will nearly always become possible to use the microscope regularly in the remaining doubtful cases. As, however, the parasites of malaria rapidly decrease or disappear from the peripheral blood within a day or two of the exhibition of

quinine, it is essential to make a blood slide immediately the patient comes under observation *before the drug is given*, in case it may be necessary to examine it for the organism a few days later if the nature of the case is not by that time clinically evident.

A blood film prepared and stained as described on p. 255 should first be briefly examined with an ordinary high-power lens (about $\frac{1}{8}$ in.). By looking along the edge an approximate idea will be obtained as to whether the leucocytes are about normal in number or are markedly increased or decreased. Any marked excess of large mononuclears will also be detected, and may strengthen a suspicion of the case being malarial. Further, after some experience, the larger forms of the benign tertian and quartan parasites, as well as crescents, may be recognized scattered near the edge of the film, where they are always found in the largest numbers. It will be remembered that Laveran discovered and described these organisms without the aid of an oil immersion lens. If any parasites are found in this way they should be confirmed by examination with $\frac{1}{2}$ -in. immersion lens, or if not seen with the lower magnification, a careful search with such a power must be made for the smaller forms of the benign parasites and for malignant tertian rings. These will be found in all parts of the film, but are sometimes most readily seen, when few in number, at the distal tagged end of the preparation. The parasites, when well stained, are so characteristic that it is a safe rule to regard anything about which the least doubt remains in the mind as being certainly not a malarial organism. The supposed finding of parasites in a non-malarial case may give rise to serious error, as in one instance within my knowledge, in which a patient with liver abscess was sent on a sea voyage in mistake for malaria.

It is usually unnecessary to spend much time over the search, for as a general rule the organisms are present in sufficient numbers to allow of their being detected within a few minutes' examination after a little experience. Table XXIX. shows the number of parasites found by me in 200 consecutive cases classed as follows : "Very numerous" means that the parasites were found immediately, being present in nearly every field of

TABLE XXIX.—NUMBER OF MALARIAL PARASITES FOUND

	Malignant Tertiats.	Benign Tertiats.	Total.	
Very numerous	20	(1)	35	(4) 56
Numerous	54	(7)	46	(3) 100
Rather few	9	(4)	12	(0) 21
Very few	13	(9)	7	(2) 20
Crescents only	3	(1) 3 (1)

the microscope ; "Numerous" indicates that they were detected after a very short search, such as one minute or less ; "Rather few" when some search up to five minutes was necessary ; and "Very few" when only occasional parasites were seen after a search of from five to ten minutes, so that without considerable care they might have been overlooked.

We see from this table that in 78 per cent the parasites were sufficiently numerous to allow of their detection within a minute or two, while in only 10 per cent were they so

few as to necessitate over five minutes' search. The figures in the brackets indicate the number of cases in which quinine was known to have been taken before the blood was examined, while this was also doubtless the case with some others in which the point had not been noted. They show that although the parasites may be found in large numbers after some quinine has been taken, yet as a rule they are few in number after its administration; no less than 11 out of the 20 cases with "very few" parasites had been noted to have previously taken the drug. If these cases are excluded, then the parasites were "very few" in only 5 per cent of the remainder. On the other hand, cases which are undoubtedly malarial clinically are met with in which no parasites are found at a single examination of the blood. It is difficult accurately to estimate their proportion, but a careful study of my two years' records has led me to the conclusion that they constitute between 10 and 20 per cent of the total number of malarial fevers seen, the majority of the patients having taken quinine before admission; but most of them can be readily recognized by clinical methods, and especially by the temperature curves of four-hour charts. The absence of the parasites, then, should not be taken as evidence of the case not being malarial if it presents the typical characters of that disease, especially if quinine has been taken before the microscopical examination.

CHARACTERS OF THE DIFFERENT VARIETIES OF MALARIAL PARASITES

1. **Quartan.**—The coloured plate in the frontispiece illustrates the different forms of protozoal parasites found in Indian fevers. They have been drawn from original specimens, all stained by Leishman's modification of Romanosky's stain. The third and fourth lines show the different stages of the quartan malarial parasite. Beginning with the earliest ring stage (No. 1 of line III.) note that it is free from pigment and in general resembles the same stage of the tertian forms. The chromatin body (stained red), however, is usually larger and more centrally situated than in the other forms. As the parasite grows it tends to spread out across the corpuscles and soon develops coarse dark sepia-brown pigment granules, which are much more conspicuous than those of the tertian forms. The chromatin body now appears as a thick oblong patch, and the whole organism very often forms a broad bar right across the red corpuscle, as in Figs. 5 to 7 of line III., which represent the stages seen on the second day of their development. On the third day they still further increase in size until they nearly completely fill the corpuscle, little or none of it remaining unstained. Then the chromatin body divides up as in No. 3 of line IV., the pigment collects in the centre and the parasite divides into six to eight spores as in Figs. 5 and 6 of line IV. Instead of forming spores, some of the parasites become larger still and constitute the gametes (corresponding with the crescent bodies of malignant tertians), which develop into the sexual stage in the mosquito's stomach. Fig. 4 of line IV. shows one of these forms. The sporulation takes place in a single infection on the third day at the time of the rise of temperature, which is apparently due to toxins set free with the breaking up of the parasite. The pigment escapes into the blood, and is taken up by the leucocytes, and especially by the large mononuclears. These pigmented leucocytes are diagnostic of malarial fever, and may rarely be found when the parasites have

disappeared, but it requires some experience to recognize them with certainty. The red corpuscles in which quartan parasites are developing do not undergo any marked changes, being neither enlarged nor containing red staining dots, known by the name of Schuffner's dots, as in benign tertians.

2. Benign Tertians.—The first two lines of the plate illustrate the different stages of the benign tertian parasites, which in turn present characteristic and easily recognized features. The earliest stage is again a small ring form, as in Figs. 1 to 6 of line I., the chromatin dot being also usually situated within the organism, while some of the rings may occupy one-third the diameter of the corpuscle, being larger than those of the malignant tertian. As they increase in size they have an irregular amoeboid appearance with very fine pigment, which is not very clearly seen if the staining is dark. The chromatin body is now larger and more or less centrally situated. When they reach the full size on the second day they occupy about two-thirds of the diameter of the red corpuscle, as in Fig. 3, line II.; the corpuscle, unlike those containing quartan parasites, becomes enlarged and paler than normal. At the end of the second day, at the time of the febrile paroxysm, they divide up into 12 to 15 spores, and then present the appearance seen in Fig. 5 of line II., while Fig. 6 shows one in which the parasite has just broken up into separate spores, setting free the pigment from between them, a rare and beautiful microscopical appearance. Another most important feature of the benign tertian parasite is the fine red stippling, known as Schuffner's dots, affecting the substance of the red corpuscle outside the parasite itself, which is shown in most of the illustrations of this form. It is well brought out by Romanosky stain, although it may be absent in the youngest ring forms. It is quite conclusive in the diagnosis between the benign tertian and the quartan, which otherwise may closely resemble it in some of its stages.

As the majority of benign tertian fevers are produced by a double infection, at any rate in the early cases seen among European patients, all the stages of the parasite are generally found in a single blood specimen, while with a good stain the Schuffner's dots are readily seen in some of the first-day forms; so that there is usually no difficulty in differentiating this parasite from the small rings of the malignant tertian variety which have no Schuffner's dots, and in which the larger forms are rarely seen in the peripheral blood. The large gamete form of the benign tertian is shown in Fig. 4 of line III., and corresponds with the crescents of the malignant form.

Malignant Tertian.--Lines V. to VII. of the plate illustrate the malignant tertian variety. The earliest stage is again a small ring, but it differs from those of the benign forms by being nearly uniformly of a very small size, about one-sixth to one-quarter of the diameter of a red corpuscle. The chromatin material occurs in the form of one or two small dots, which are situated at the edge of the ring and tend to project slightly outside its edge in a manner not seen in the benign forms of malaria as A. Powell has pointed out. Not infrequently two or more rings may be found in a single corpuscle, while Fig. 6 of line V. shows no less than 5 parasites in one red cell in an extraordinarily numerous and rapidly fatal infection with more parasites than corpuscles. As a general rule only these small ring forms are seen in the peripheral blood, so that when a number of such rings, without any larger forms, are met with, the infection is practically always a malignant tertian,

this being, indeed, the most distinguishing feature of the blood in this form of malaria. The reason of this distribution of the parasites is that there is a marked tendency for the red corpuscles infected by them to become shrunken and irregular and to present a crenated appearance, such as that illustrated in line V. of the plate. This in turn causes these infected corpuscles to act as foreign bodies and become sifted out in the spleen, bone marrow and liver, so that by the time the larger second-day forms are reached they have accumulated in these organs, where they may be found in very large numbers in fatal cases. When the number of parasites is exceptionally large, then some of these later stages will be found in the peripheral blood as well, those shown in line VI. of the plate having been drawn from the very intense infection just mentioned. Figs. 2 and 3 of line VI. show the full size to which this form of parasite attains, namely, about half the diameter of a red corpuscle only. The pigment is fine as in the benign tertian, but usually more scanty than in that form. Before sporulation it collects in the centre of the parasite, as in Fig. 5 of line VI., which then divides up into about a dozen spores, as in Figs. 5 and 6 of the same line.

Instead of dividing up into spores the parasite may continue to enlarge and then elongate out, as in Figs. 7 and 8 of line VI., and thus develop into the crescent-shaped gametes of line VII. As these elongate they stretch out the red corpuscle until its remains appear as a bluish or reddish line across the concavity of the crescent, as in Fig. 4 of line VII., and eventually this disappears, probably by rupturing, and the free crescents of Figs. 6 and 7, line VII., are formed. The distribution of the pigment in these gametes varies with their sex, being concentrated in the centre, often in a ring-shaped form, in the female gamete, as in Fig. 4, line VII., which after extruding two polar bodies, becomes fertilized in the mosquito's stomach by the flagella, or, more correctly speaking microgametes, set free from the male gamete. The latter is distinguished by having its pigment more uniformly distributed through the crescent, as in Figs. 2 and 6 of line VII. In recent infections these crescent bodies are not seen, but about a week or ten days later in insufficiently treated cases they may develop, and they form the most characteristic and easily recognized kind of malignant tertians. In my European series, however, they were only found in 10 per cent of the cases, and in only three of these were the ring forms not seen, so that it is but occasionally that they materially assist the diagnosis.

In addition to the shrunken, irregular appearance or crenation of the red corpuscles infected by malignant tertians, they may show in fresh unstained specimens a darker colour than normal, which has caused them to be termed "brassy" corpuscles. This is in marked contrast to the enlarged pale corpuscles of benign tertian infection, and the unaltered condition of quartan ones: the red corpuscles containing malignant tertian parasites may all stain a different tint from the uninfected ones. Further, in very well stained specimens a scanty coarse red stippling, known as Marshall's dots, may be seen, as shown in Figs. 1 to 5 of line VI. This has to be carefully distinguished from the copious fine stippling of benign tertians.

The Mosquito Cycle of Malarial Parasites.—The stage of the life history of the malarial parasites which takes place outside the human body is of more epidemiological than clinical interest, but may be briefly mentioned for the sake of completeness. It is shown diagrammatically in the Frontispiece. After the fertilization of the female gamete in the

stomach of a mosquito the zygote thus formed elongates out into a vermicule, or ookinete, and burrows into the wall of the stomach, in the outer layers of which it forms an oocyst by the secretion of a sheath around it. The nucleus undergoes multiple division to form a number of sporoblasts and a residual body. The spores further subdivide to form small elongated sporozoites, which eventually escape with the rupture of the cyst wall into the body cavity, and find their way to the salivary glands, from which they are injected at the time the infected mosquito bites, thus they get back to the original host, and enter the red cells to form small ring parasites once more. The mosquito cycle usually takes about eight to ten days for its completion under favourable temperature conditions, but if the air is somewhat colder than the optimum temperature, the development takes longer, while below 16° no development takes place. The development only takes place in anopheles, not in culex. The difference between the two classes is shown in Plate 9. The most important points to note are that in anopheles the proboscis is in a line with the long axis of the body, while in culex it is bent at right angles. The former, except when very full of blood, or in some forms such as culicifaciens, stands with its back at an angle with the surface, while in the case of culex the back is parallel to the surface.

The Etiology of Relapses.—The question as to what particular stage of the life history of malarial parasites is responsible for bringing about relapses has given rise to great differences of opinion, and the controversy is far from being settled. The essential point in dispute is whether some of the asexual stages of the parasites remain in the system for long periods in too small numbers to produce fever and bring about a relapse when for some reason, such as lowered resistance of the patient, they are able to multiply rapidly again; or whether some specially resistant form, either the gametocytes of the sexual cycle or peculiar conjugation forms, remains latent in the system and by parthenogenesis of the gametocyte or subdivision of the conjugation forms reproduces young trophozooids which invade the red corpuscles and produce the relapse. From the zoological standpoint the former is the simpler and more natural occurrence, and very strong evidence is required before either of the latter more complicated processes can be accepted.

Parthenogenesis implies that an unfertilized ovum, or virgin female gamete, under certain conditions reaches exactly the same stage of development as a zygote, or ovum conjunct with a male gamete, but the unfertilized female gamete develops into a progeny of sporozooids. In putting forward this theory Schaudin invoked a phenomenon which, so far as is known, is unparalleled in biology, and so is a phenomenon that demands very ample confirmation (A. Alcock). In 1903 Schaudin described forms in which the nucleus of the macrogamete divided into two portions, around the larger of which pigment-free protoplasm collected; it then divided like the nucleus of a schizont and formed merozooids which infected fresh red corpuscles. This view has been supported by Harrison and by Karrewij (1909), Swellengrebel, Acton and Knowles (1913) and others. On the other hand, good authorities, such as Ronald Ross, Bignami (1913), W. M. J. James (1913), and J. D. Thomson (1917), all consider the evidence is quite inadequate to support such a far-reaching and improbable theory.

Conjugation forms have been described by C. F. Craig as the cause of relapses, which he believes are formed by the conjugation of two schizonts within a red corpuscle, pro-

ducing a resting stage resistant to quinine and other harmful influences, which lies dormant until under more favourable circumstances it gives birth to several young plasmodia producing a relapse. This ingenious theory has received very little support.

There remains the simple explanation of the survival of some of the asexual stages of the parasites for long periods, and the enumeration studies of Ronald Ross, J. D. Thomson and D. Thompson have shown by a study of thick-film preparations that this stage of the organism may be found in small numbers throughout intervals of apyrexia, and thus readily account for the relapses. Further, D. Thompson has brought forward evidence to show that the life of gametes is not more than twenty-one days, as under efficient quinine treatment they die out in three weeks, their persistence for longer periods being due to their continued development from surviving schizonts. Their observations are greatly against the parthenogenesis theory, and in favour of Ross's more simple contention that relapses are brought about by the survival of a few of the asexual stages of the parasites, which appears to be the more likely explanation of relapses.

Cultivation of Malarial Parasites.—In 1912 C. C. Bass and F. M. Johns reported the successful cultivation of malarial parasites under anaerobic conditions in defibrinated blood, of which 10 c.c. were added to $\frac{1}{10}$ c.c. of a 50 per cent solution of dextrose in tubes forming a column not less than 2 inches in depth and kept at 40°C . The plasmodia multiply in the upper layers of the corpuscles beneath the supernatant serum. They obtained multiplication and development of the parasites to at least four generations if the leucocytes were removed. This interesting observation was soon confirmed by J. D. Thomson, D. Thompson and McLellan, H. Ziemann, de Roche, Lima, Werner, Sergent and many others. In 1914 Bass described special apparatus for facilitating the cultures; this apparatus has been simplified by Row. L. Dudgeon and C. Clarke found malarial parasites by culture in 7 out of 10 cases in which they could not be detected in ordinary films, showing that the method has some diagnostic value.

Unusual Forms of Malarial Parasites.—In addition to the three classical varieties of malarial parasites, various workers have described and even named what they considered to be special forms, but experts differ greatly regarding their claims to recognition. A quotidian variety has long been suspected, and is recognized among others by Craig as occurring in both pigmented and unpigmented forms. Stephens described from a single slide sent from India what he thought was a new malarial parasite with scanty cytoplasm and extreme amoeboid movement, but his conclusions were severely criticized by A. Balfour and Wenyon, who have met with similar forms in sub-tertian malaria. A. Emin described a parasite resembling benign tertian, but with fewer merozoites and gametocytes; this parasite does not enlarge the host cell, and Craig records having met with a similar organism in the Philippines.

MALARIA-CARRYING MOSQUITOES

In the prophylaxis of malaria in different countries the most essential knowledge is what particular anopheles are responsible for carrying the infection. In the past much time and money has been wasted in combating varieties of mosquitoes which are now

FEVERS IN THE TROPICS

TABLE XXX.—INDIAN MALARIA-CARRYING ANOPHELINES

Variety.	Breeding-Places.	Distribution.	Forms of Malaria carried by it.
A. barbirostris (Van der Walp)	Shady pools and water-courses. Rarely enters houses.	All India except N.W. Frontier.	M.T. exp. (Walker).
A. culicifacies (Giles)	Sluggish streams, fresh rain water, irrigation channels. Common house species.	Burma, Assam and all India south to Madras. Not in Ceylon. Up to 3000 ft.	All forms experimentally. Most important carrier in India.
A. fuliginosus (Giles)	Swampy water and pools with much vegetation. Occurs in houses and cattle-sheds.	All India and Burma, up to 5000 ft.	All forms experimentally. Naturally infected, but not good carriers.
A. funestus var. listoni (Liston)	Streams. Common in houses. . . .	All North India and Burma, Central India, west coast and Ceylon.	Naturally infected.
A. ludlowii (Theobald)	Near sea coast in brackish water. Frequents houses.	Burma, Andamans, Madras and Ceylon.	Found infected naturally.
A. maculatus (Theobald)	Streams and river beds near the hills.	N.W. Himalayas, Assam, South India and Ceylon.	M.T. experimentally, and infected naturally.
A. maculipalpes (Giles)	Pools, often in connexion with hill streams. Occurs in houses.	N.W. Frontier, Indo-Gangetic Plain, Himalayan Terai, Central India, west coast and South India.	M.T. experimentally, and infected naturally.
A. minimus (Theobald)	Streams and ponds. Occurs freely in houses.	Assam, Bengal, and rarely in Central India.	M.T. experimentally, and infected naturally.
A. rossii (Giles)	Pools of rain water. Abundant in houses and cattle-sheds.	All North India, Burma, Ori-sa, Central and South India and west coast.	All forms experimentally. Not good natural carriers.
A. stephensi (Liston)	Pools of river beds and streams. In pots, cisterns and wells. Occurs in houses.	Burma, Bengal, Central and South India, west coast, Indo-Gangetic Plain and N.W. Frontier.	M.T. and Q. experimentally. Infected naturally. Important carrier.
A. willmoii (James)	Stream breeder. Found in houses and cattle-sheds.	Himalayas, up to 6000 ft. from N.W. Frontier to Assam.	Naturally infected.

known not to carry the disease. By first working out the natural carriers, and then finding their breeding-places, such waste will be prevented, and any possible reduction in the numbers of the incriminated insects can be carried out with the minimum expenditure. The question has been most completely worked out in India, and the important data are shown in the table which has been compiled from a detailed paper of S. R. Christophers (*Ind. Jour. Med. Research*, Jan. 1916). All the varieties of anopheles which have been proved by feeding experimentally or found naturally infected are given, together with their distribution in India, their breeding-places and habitat. They number only eleven out of thirty-eight Indian species recognized as valid by Christophers.

In the **Malay States** Stanton has made a similar study and gives the following as carriers of malaria in the East. In the Federated Malay States, *A. maculatus*, *nigrans*, *umbrosus*, *fuliginosus*, *albirostris* and *simensis*. In Sumatra, *A. rossi*, and in Formosa, *A. listoni* (now called by Christophers, *A. funestus*, var. *listoni*), *annulipes*, *simensis* and *formosaensis*, while Zassi also gives *maculatus* and *willmoi*. In the Philippines Walker and Baber showed by careful work that *A. febrifer* is the principal carrier, and *A. rossi*, *maculatus* and *barbirostris* play a small part. In addition to the above, Castellani and Chalmers give the following as proved carriers in the East. In Cochin China, Cambodia and Tonkin, *A. vincenti* (Laveran), *A. minimus*, *A. martini* (Laveran), *A. pursati* (Laveran). In the New Hebrides, *A. foranti* (Laveran), and in New Guinea, *A. punctata*. In Australia, Taylor incriminated *A. annulipes* in the Murray River district.

In **Arabia**, Gill found *culicifacies*, *funestus* and *stephensi* to be the carriers.

In **Africa**, *Pyretophorus costalis* appears to be the principal carrier, together with *M. funesta* (Giles), in West Africa, *A. zeemani* (Grunberg), *A. pharoensis* (Theobald), and in Madagascar, *M. constani* (Laveran).

In **America**, F. Knabb gives the following eight carriers out of thirty-four recognized species. *Albimanus*, *argyritarsis*, *crucians*, *intermedium*, *quadrimaculatus*, *pseudo-** *maculipes*, *pseudopunctipennis* and *tarsimacula*. The first two are also carriers in St. Lucia (Nicholls). In the Panama Canal zone Darling found *A. albimanus* the principal carrier, and to a less extent *tarsimacula* and *pseudopunctipennis*. In Venezuela, *A. crucians* has been implicated by Rincones in addition to *argyritarsis* and *albimanus*.

In **Europe**, Castellani and Chalmers record the following carriers : *A. maculipennis*, *A. bifurcatus*, and in Italy, *A. superpicta* (Grassi) and *A. pseudopictus* (Grassi).

THE PROPHYLAXIS OF MALARIA

In few diseases is it more true that prevention is better than cure than in malaria, for although it is easy to cut short an actual attack, yet it is often exceedingly difficult completely to eradicate the infection from the system. The study of this aspect of the question is in itself the work of a lifetime, and its full discussion is far beyond the scope of this work, while it has been so admirably dealt with in the writings of Sir Ronald Ross

and other authorities that it is superfluous for me to attempt it. Only the main principles will therefore be briefly mentioned.

There are three different ways in which the infection of malaria may be prevented in any community. Firstly, by destroying all or nearly all the anopheles which can convey the infection from man to man, or preventing infection through them by the use of mosquito curtains ; secondly, administering quinine with sufficient frequency to prevent the development in the human system of any infection which may be introduced ; and thirdly, to destroy all infection in the whole population by prolonged and universal drugging with quinine as suggested by Koch.

The Destruction of Anopheles.—The first method of mosquito reduction has been successfully used in certain favourable places, such as Ismailia in Egypt, with low rainfall and limited breeding-grounds, which can be permanently dealt with at a comparatively low cost by drainage and levelling operations, and when practically unlimited funds are available in connexion with a large commercial undertaking, as in the case of the Panama Canal. A year's careful study of the breeding-grounds in the suburbs of Calcutta showed me that the hundreds of miles of unlined roadside drains, which it was not practicable to keep continuously oiled, and would be very costly to level and line with cement to prevent water standing in them, produced abundant malaria-carrying anopheles throughout the rainy season. Anti-mosquito measures are still more impossible in rural areas of Bengal and most parts of India where malaria is especially prevalent. On the advice of the Royal Societies' Malaria Commissioners, and under the direction of one of them, a test experiment was carried out by the Government of India at Mian Mir, the malarious cantonment of Lahore for several years ; but the results were very disappointing, although the area dealt with was extended considerably beyond the distance at first advised, and canal irrigation stopped with the resulting loss of many trees ; and the measure has been abandoned. Nevertheless, surface drainage is undoubtedly a most important anti-malarial measure in towns and in municipal areas as shown by the fact that Calcutta a few decades ago was very malarious, and after it was properly drained became far more healthy, so that its malarial endemic index is now nil. Ever since 1901 I have advocated for all municipal areas in malarious districts the preparation of a complete surface drainage scheme, the outfall to be first constructed and the system extended year by year as funds are available until it is completed ; but little has yet been accomplished on these lines in India.

The method of destroying mosquito larvae in their breeding-places by the weekly application of kerosene oil and other preparations is often of value, although it has the grave disadvantage, as compared with a proper surface drainage system, of entailing unending expenditure without any permanent benefit.

Mosquito Protection.—This takes the form of either rendering houses mosquito proof by means of fine wire netting, as successfully carried out in Italian railways, or sleeping under mosquito-proof nets, as advised by Annesley in 1828 as a preventive of malaria, and for long used in India and other tropical climates to avoid the disturbance and annoyance caused by these ubiquitous pests. Mosquito-proof houses have also been advocated for India, but in most parts the great heat prohibits their use owing to their cutting off

(Plate 9).—Adult and larval forms of *Ampelophiles*.



the eagerly welcomed breezes. It is only in the most malarious parts without extreme heat, such as portions of Assam and the Duars, that they might be worth trying.

The Mosquito Curtain is a measure which should never be neglected by Europeans in malarial parts of the tropics, as it furnishes the simplest method of protection from infection, and, if attention is paid to the nets being in good repair and carefully tucked in under the mattress, they are very efficient during the dangerous night period, when anopheles are most active. Either boots or two pairs of socks are a useful protection against bites on the ankles in the evening, while gloves and leggings have been advised in intensely malarial places, but they are not necessary in most parts of India.

Segregation of Europeans from the Native Population.—Since it has become known that in highly malarious places a large proportion of the apparently healthy indigenous population harbour malarial parasites in their blood, from whom mosquitoes become infected and carry the disease to Europeans, the separation wherever possible of houses inhabited by European immigrants from native huts by a distance of from one quarter to half a mile, has become a most important prophylactic measure, which is specially applicable to railway construction and other temporary camps or in planning new towns.

QUININE PROPHYLAXIS IN MALARIA

The administration of quinine as a prophylactic against malarial infection is the most easily and universally applicable method, as it can be used under the numerous conditions in which the destruction of malaria-bearing mosquitoes or mechanical protection against their bites is quite impracticable, for example, during military operations in malarious areas. Unfortunately, the greatest differences of opinion still exist both as to the value of quinine given prophylactically and regarding the doses and frequency of administration. A good deal of this confusion has resulted because the nature of the problem has not always been clearly grasped. In consequence, the fact that different measures are required for treating the different types of the disease which occur in various countries has not been realized. The principles on which quinine prophylaxis should be based will therefore first be considered, and the recently recorded successes and failures with different methods of quinine prophylaxis will then be discussed, and conclusions drawn as to the best methods under different circumstances.

The Principles of Quinine Prophylaxis.—In the first place a clear distinction must be drawn between the prevention of a primary infection by taking quinine during residence in a malarious area and the prevention of relapses in a person already infected, for much larger and more frequent doses are required to eliminate an old-established infection and prevent relapses than to prevent an original infection. As long ago as 1896 I showed that when a regiment infected with malaria is transferred to a comparatively healthy place a large proportion of the malarial cases occurring in it during most of the year are relapses, and the same is doubtless the case to a large extent in jail populations. As most of the recorded trials of quinine prophylaxis in India have been made in regiments and jails this aspect of the question requires much closer attention than it has yet received.

Secondly, malaria differs much in severity in different countries, while the various types have different incubation periods ; this should be taken into account in deciding on the frequency of the doses, as clearly pointed out by H. Acton. Thus, benign tertian and the rarer quartan malarias with mean incubation periods of eleven and fourteen days, and a minimum of six and eleven days respectively, are more easily prevented than the much severer malignant tertian malaria with a mean incubation period of six days and a minimum of even as little as two days. Further, malignant tertian malaria of many parts of Africa is undoubtedly a much more severe and dangerous infection than that met with commonly in India and most other parts of the world, its very frequent complication with blackwater fever being also associated with this greater severity. Recent war experience also seems to show that it may be more resistant to quinine both prophylactically and curatively, so that prophylactic doses which might succeed in the case of comparatively mild infections of other countries may well prove less effective against the malignant pernicious African form, although there is evidence to show that even when the disease is not completely prevented its severity is often greatly mitigated by regular quinine prophylaxis. Another important principle to be borne in mind is that a single dose of quinine is almost completely eliminated from the system within forty-eight hours.

Methods of Quinine Prophylaxis.—**1. Large Doses once or Twice a Week.**—The authority of Koch has led to the wide adoption of his method of giving 10 to 15 grains of quinine on two consecutive days once a week. This method has been reported on favourably by Herrick in European troops in Sind, 15-grain doses being given in solution, and commenced some months before an epidemic is expected ; by Graham in school children in the United Provinces of India, where it was very popular ; by Engeland on board ship of South-West Africa in half-gramme doses every second or third day. Ziemann and Nocht advise a slight modification, namely, 1 grammie in 0·25-gm. doses every fourth day. On the other hand, failures of this method have been recorded by Manteufel, who reports on twelve years' experience of Koch's method at Dar-es-Salaam in East Africa, where neither the case incidence nor the mortality from malaria and black-water fever had fallen during that period of time ; by Huddleston in the case of the British Army in India, and by Werner in South-West Africa. Granada records the interesting experience that 0·8-gm. doses bi-weekly, on Wednesdays and Saturdays, in the Malay Straits reduced benign tertian and quartan malaria, but had very little effect on the malignant tertian variety. Wooley and A. R. S. Anderson independently failed with 10 to 15 grains bi-weekly in the Andaman Islands, and the latter also in the Dacca Jail in Eastern Bengal, while Stott had a similar experience in the Mandalay Jail in Burma and Gill in Arabia. The balance of recent evidence is thus clearly against Koch's method, especially in very malarious places such as Africa and the Andaman Islands.

2. Small Doses Daily.—The plan of giving 5-grain doses of the sulphate daily, or 4 grains of the hydrochloride of quinine, has also been extensively tried with somewhat contradictory results. Thus, good results have been reported from Uganda, where this method gave better results than larger doses bi-weekly ; by Bouffard in Senegal, who used .25 gm. of the hydrochloride ; by a French Commission under Bertrand in the French Colonies, who used the same salt ; by Parrot in schools in Algeria, who gave 0·2-gm. doses

of the bi-hydrochloride to children of five years and upwards, which proved much more popular and satisfactory than chocolate and tannate of quinine tablets ; by Henson in America ; by Hebir in India, who also advises one 10- to 15-grain dose once a week if malaria is severe. Ziemann also prefers small daily doses to larger ones twice a week because the drug is all excreted within three days, while C. A. Gill advises quinine to be given not less frequently than every other day as it is eliminated in forty-eight hours, while in highly endemic tracts the daily dose should be not less than ten grains, and he reports good results at Muscat under military conditions.

On the other hand this method failed in the hands of Ryley among European troops at Hongkong ; McGuire in the West Indies found 5- to 8-grain doses retarded the development of malaria and masked it, but did not completely prevent it, and he does not advise it as a routine measure, although it should be used in 5 to 10 grains daily during a short campaign in a malarious country ; Linnel in the Malay States found that neither 5-grain doses, nor any quantity on which a coolie could do his work, would stop malaria in unhealthy areas, although interrupted use of quinine did much to prevent malaria taking a serious form.

The foregoing evidence is much more favourable to the method of small daily doses of quinine than to that of bi-weekly larger doses, and although the daily doses may fail materially to diminish the incidence of malaria in very badly affected countries they lessen the severity of the disease and the consequent mortality and serious complications, including pernicious cerebral malaria and blackwater fever, and render malaria easier to deal with in very unhealthy tracts of country, as has been pointed out by Waldow and others.

Other Suggested Methods of Quinine Prophylaxis.—Two other suggestions are worthy of consideration. In the first place, D. Thompson, as a result of very extensive investigations of malaria, thinks that small daily doses of quinine may tend to produce quinine-fast parasites with greater difficulty in curing the cases, and he is supported in this view by some other workers. He therefore advises that curative doses, such as not less than 20 grains a day for three weeks, should be administered every quarter of the year. In places with very high endemic indices, such as many parts of Africa, the Malay States and parts of India, such as the Duars and portions of Assam, the vast majority of the indigenous inhabitants are already infected with malaria, and small prophylactic doses cannot be expected to be of any material value. Thompson's suggestion is well worthy of trial, while it is noteworthy that it is just in such places that the ordinary methods of quinine prophylaxis have often failed, not because new infections cannot be prevented by adequate prophylaxis, but because such doses are ineffective against established infections.

The other suggestion is that of Acton, based on the incubation periods of malaria and the necessity of getting sufficient quinine into the system at least forty-eight hours before the infection may develop into a paroxysm of fever. By deducting two days from the mean incubation periods of the different forms of malaria already noted he concluded that to be effective prophylactic quinine should be given at least every eleven days in quartan, eight days in benign tertian and four days in malignant tertian malaria respectively. As the malignant tertian form is the most common in most countries, including all the more

highly malarious ones, it follows that four days should be the longest interval between the doses. The comparative failure of Koch's method, especially in Africa, where malignant tertian malaria so greatly predominates, is thus readily explained. On the other hand, there is good reason for believing that 5-grain daily doses may be insufficient in very malarious places and especially against the more resistant African forms of malaria. Acton suggests 5- to 10-grain doses on two consecutive days (so as to deal with double infections), every eight days for benign tertian malaria, to which may be added the much rarer quartan form, but that for prophylaxis against malignant tertian malaria 10- to 15-grain doses should be given on two consecutive days every fourth day. During epidemics, when the incubation period may be reduced to as little as two days, the interval between the doses should not exceed two days. This is in close agreement with Gill's success in Arabia with 10-grain doses every other day. These methods are certainly worthy of careful trial in view of the frequent failure of the older plans. Personally I took 10 grains of quinine daily in 1896 when working in parts of Assam with an endemic index of 80 per cent, and did not even use a mosquito net in those pre-mosquito malarial days, although I should do so now in addition to the quinine.

Curative Quinine Treatment of the Malarious to lessen the Sources of Infection.—

It is obvious that if all primary infections were rapidly and efficiently treated so as to cure them before gametocytes had time to develop the anopheles mosquitoes would become harmless, as no opportunities of their becoming infected would remain. This is usually a counsel of perfection, yet something has been accomplished on these lines in certain places. Thus Hatori records an anti-malarial campaign in Formosa in which the blood of all the inhabitants was examined microscopically for malarial parasites and all those found infected were treated with quinine for thirty days. One expert could examine eighty blood films a day, and in a little under three years 409,355 examinations were made with 2.83 per cent positive results. A great decrease in the parasitic indices and the fever rate has occurred and in some parts no malaria has been reported for two years. The people who had at first opposed the measure are now thankful for it. The cost was elevenpence per case treated, and the method has now been made compulsory by ordinance all over the island. N. Barlow has also reported such a campaign on a fruit farm in Honduras, where over half the labour force was infected. The microscope was used for diagnosing. All the cases were treated with 20 to 30 grains of quinine for two days, followed by 15 grains daily for one month, and twice a week for two months more in malignant tertian cases. No relapse occurred among 218 patients who took the full three months' course, while every one of 116 cases who left off the drug after only one month relapsed. He considers that if importations are few the disease can be stamped out by this method.

CLINICAL DESCRIPTION OF MALARIAL FEVERS

The following account of malarial fevers is mainly based on an analysis of the records and charts of some 200 consecutive cases in which malarial parasites were found by me in two years' records at the European General Hospital, Calcutta, Captain Megaw's

account and tables of malaria simultaneously examined at the Native Medical College Hospital being also frequently referred to.

HISTORY OF THE ONSET OF THE DISEASE

On admission of a patient suffering from fever the following points in the history of the case may be of some use in assisting the diagnosis.

Duration of Fever before Admission.—In three-fifths of my malarial cases the fever had lasted less than seven days, but in the remaining two-fifths it had been present for eight or more days, which would nearly absolutely exclude seven-day fever described on page 294. A long history was more frequent in benign tertians and quartans than in malignant tertians.

Rigors.—Ague, or shivering fits, at the onset is one of the most characteristic features of malarial fevers, and especially so when it recurs at regular intervals of two or three days. It may also occur in any fever in the tropics, not excluding typhoid itself, while it is very common at the beginning of seven-day fever, although only exceptionally is it repeated in that disease. The history obtained of the occurrence of rigors may vary much in malarial fevers as shown in Table XXXI.

TABLE XXXI.—RIGORS IN MALARIAL FEVERS

	Malignant Tertians.	Benign Tertians.	Total.
Rigors noted to have been absent . . .	8	4	12
Rigors recorded but frequency not noted	29	41	70
Rigors occurring daily	22	25	47
Rigors every other day	14	18	32
Totals	73	88	161

Rigors have thus most frequently been recorded as present daily, especially in double benign tertians and more rarely in quotidian malignant tertians.

Some of the older Indian writers lay much stress on the diagnostic value of the greater frequency with which the rise of temperature occurs in the morning in malarial as opposed to other fevers. This was found to be borne out by such of my cases as this point was recorded in, for in 22 the rigor came on in the forenoon, in 12 between noon and 8 P.M., and only in 9 during the evening or night. Megaw also notes that the hour of onset of the fever is uniformly in the forenoon or early afternoon. It may occur in the evening, but only very exceptionally in the night or early morning. In this last respect malarial fevers differ from kala-azar, in which rises often occur in the early morning hours, especially during the double remittent type which is so characteristic of this disease (see Chart 3, p. 26). I have never seen a double daily rise in a malarial fever, although Megaw obtained a history of it in one case of mixed malignant and benign tertian infection. The

shivering fit in malaria usually lasts about half an hour, but may continue for an hour or more, especially in malignant tertians.

Headache.—After rigors, headache is the most frequently mentioned symptom, and was rarely noted to be absent. It was occasionally severe, but variable in its position, and seldom presented the severe frontal type with pains in the back of the eyes which is so constant in seven-day fever. It was more frequently noted in the malignant than in the benign tertian forms.

Pains in the body and limbs were also frequently noted in malaria during the fever, but were nothing like so constant and severe as in seven-day fever.

Sickness and Nausea are very commonly present in malarial fevers, having been noted in about three-fourths of the malignant tertians and in half the benign cases; they probably occurred in a still further number in which they were not recorded. This symptom is less frequent in the seven-day fever, in which it was noted in only one-fourth of the cases.

CONDITION ON ADMISSION

There is nothing very characteristic about the general appearance of a malarial patient, but the following points may be noted on examination.

The Tongue shows furring very frequently, but commonly of only slight degree. The furring is uniform in its distribution, and thus differs from that seen in the red-edged tongue of typhoid and seven-day fever: a point which I have frequently found of great service in the clinical differentiation of the latter disease from malaria.

The Pulse Rate is also of great value for the same purpose, for in malaria it *very seldom shows a slow rate* accompanying a high temperature, as is so frequently the case in seven-day fever, especially in the malaria-resembling terminal type (see p. 296). Out of 49 malarial cases with pulse records, in only 5 was the rate noted as being under 100 with a temperature of 103° or over, while in only 3 more was it between 100 and 109. In all the other cases the pulse registered 110 or over with such temperatures, a rate which is practically never seen in seven-day fever, except very rarely just after the onset of the fever and before rest in bed has been obtained, but never, in my experience, during the terminal rise which otherwise closely simulates malignant tertian malaria. A rapid pulse, then, is almost diagnostic of malaria as against seven-day fever, and attention to this point will prevent the common error of returning the terminal cases of seven-day fever as malarial.

The Lungs very rarely show any abnormal physical signs in malaria, pharyngitis and bronchial catarrh being especially uncommon in this fever, as compared with influenza and typhoid. Serious lung complications, such as pneumonia and pleurisy, are equally rare in Bengal, but in colder parts, such as the Punjab with bitterly cold winds in the winter season, malarious subjects are very liable to be attacked with pneumonia, and Hay Burgess described cases with remittent fever and high large mononuclear count,

without any increase of the polynuclears which he attributed to malaria, although the only examination of the sputum recorded showed pneumococci.

The Heart is also very seldom affected by any inflammatory complication in this disease, although in chronic cases after repeated attacks with marked anaemia haemic murmurs may be detected.

The Bowels are commonly constipated, so that a purge is generally indicated, although quinine does act efficiently in a true malarial fever even during constipation. Occasionally severe diarrhoea may occur in malaria, which may rarely be so severe as to be mistaken for cholera. When working at the blood changes in cholera, I met with such a case in the cholera ward in which the absence of the leucocytosis, which is so constant in that disease, and the presence of a large mononuclear increase led me to search for, and find, malarial parasites, and the patient recovered under quinine.

The Liver was normal in three-fourths of the patients. In the remaining fourth it was enlarged, more frequently in malignant than in benign tertians. In only 2 per cent, however, did the edge of the organ reach more than 2 in. below the costal margin, against 23 per cent of kala-azar cases, so that marked enlargement of the liver is much more common in the latter disease in Europeans. In Megaw's native malarial patients enlargement of the liver was found in 20 per cent. The liver may sometimes be markedly enlarged in true malarial cachexia, and in the Punjab, where kala-azar is unknown, I have occasionally seen the liver reach down to about the navel in chronic malaria, so that too much reliance must not be placed on this point in the differential diagnosis of the two conditions.

The Spleen is more frequently enlarged than the liver in malaria. In my European series the organ could be felt below the ribs in 44 per cent, and in Megaw's native hospital one in 40 per cent. In both series enlargement was found rather more often in benign than in malignant tertians, and in the quartans in as many as 60 per cent, which is in accordance with the longer histories of fever in the latter types.

It appears, then, that in early cases of malaria the spleen is more often normal than enlarged, so that the absence of enlargement is no evidence of a case not being malarial. In 16 per cent the organ reached to from 2 to 4 in. below the ribs, while in 4 to 5 per cent it extended to the navel, or rarely beyond that point. Very large spleens are also met with in malarial cachexia in the Punjab in the absence of kala-azar, so that it is clear that although these great degrees of enlargement are very much more common in kala-azar than in true malarial cachexia, yet they may also occur in the latter disease, especially in the quartan variety, sufficiently frequently to make it unsafe to rely on such huge spleens being diagnostic of the more serious kala-azar as against malaria.

The Urine may be increased during the cold stage, and decreased and of high specific gravity after the sweating one, but it very rarely shows albumen. **Urobilin** is often present in excess owing to the destruction of the red corpuscles exceeding the powers of the liver to deal with the dissolved haemoglobin, and Atkinson and others regard Schlesinger's test for demonstrating it as of diagnostic value. Add to urine in a test-tube an equal part of a solution of one part of zinc acetate in ten parts of alcohol,

and then add a few drops of a weak solution of tincture of iodine. The mixture is then filtered and if urobilin is present a more or less distinct fluorescence is seen. The reaction may be present in some other diseases, such as liver abscess and certain infectious diseases, but its absence is much against malaria, while a positive test may indicate the presence of latent malaria.

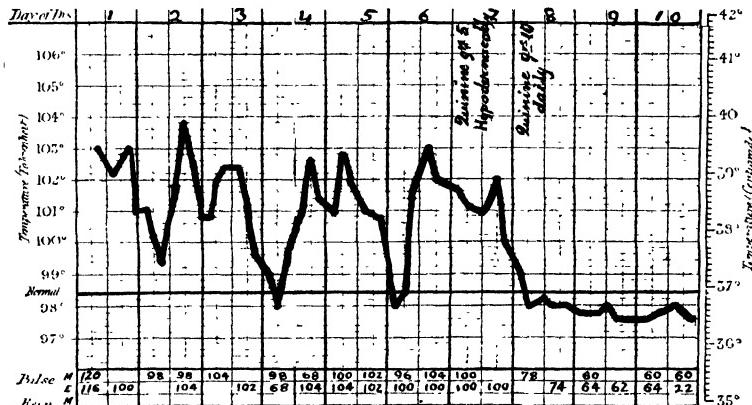
THE TEMPERATURE CURVES IN DIFFERENT TYPES OF MALARIA

The symptoms and physical signs just described are seldom sufficiently characteristic to allow of a certain diagnosis of malaria. The temperature curves, on the other hand, are for the most part so typical that they commonly enable a confident opinion to be formed not only as to the presence of malaria, but also of the variety of the disease. A lack of knowledge of the value of the temperature curves in the diagnosis of malaria has largely been the cause of so many other fevers being confused with it in India, although these types have long been familiar to European and American workers, and were, indeed, fully described, as far as was possible before the days of the thermometer, by ancient writers. The same types are met with in India at the present day, and although deviations from the normal curves do occur, yet it is not too much to say that a considerable proportion of malarial fevers can be diagnosed clinically without the use of the microscope by attention to the points about to be described and illustrated. For this purpose it is important that the temperature should be charted every four hours, the usual morning and evening records not being sufficient for bringing out the characteristic curves in the most typical manner.

TEMPERATURE CURVE IN MALIGNANT tertians

To begin with the most characteristic form of malaria, the typical chart of which can scarcely be mistaken for any other fever, we will take the common malignant tertian variety. Chart 39 shows the termination of one paroxysm, followed by three complete

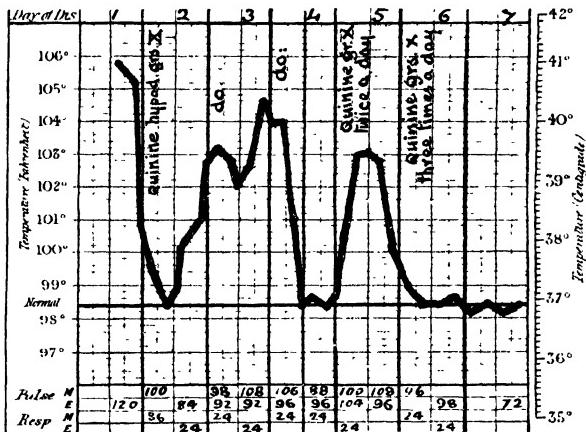
CHART 39 (Case 1371)



Malignant tertian malaria, showing three typical paroxysms, and yielding rapidly to quinine given during the last paroxysm.

ones, quinine not having been given until the middle of the last one. The important point to notice is that the febrile paroxysm lasts for from twenty-four to thirty-six hours, so that the rise of temperature takes place only every other day. The remissions are also quite short, being only of a few hours' duration, instead of twenty-four hours or more as in a single benign tertian infection. Another pretty constant feature is that soon after the initial rapid rise of temperature, which reaches 103° or 104° as a rule, there is a remission of a degree or two followed by a second slight rise, so that the top of the curve is not flat, but is broken by a short depression. The decline at the end of any paroxysm is not as rapid as the rise, but generally takes eight to twelve hours. The fall of temperature between the paroxysms may not reach the normal line, in which case the chart assumes a remittent character, or it may touch normal every other day, although

CHART 40 (Case 1214)



Typical malignant tertian malaria, showing a short abortive final rise of temperature.

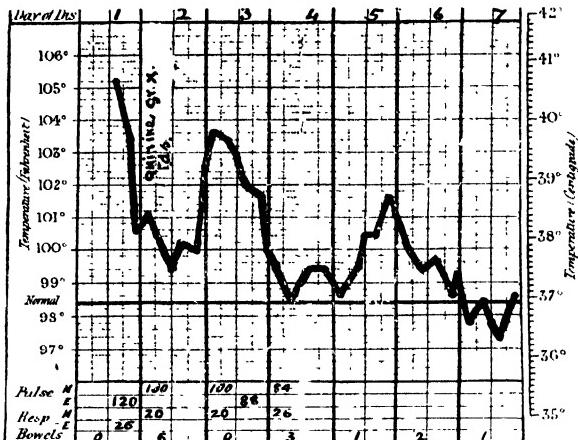
there is not as much tendency for it to reach a markedly subnormal point as there is in benign tertians. A succession of two or three such paroxysms, each extending over two days, is quite characteristic of malignant tertian malaria, and enables it to be confidently diagnosed from the chart alone. If quinine is given immediately on admission usually only one complete typical paroxysm will be seen, although it may be followed by a shorter abortive rise, such as the second complete one in Chart 40, lasting for only about twenty hours or even less. Its height also tends to become lower, as in the third paroxysm of Chart 41. The slight remission at the height of the curve may also be absent as in Chart 41, or this remission may be so marked as to reach the normal line, as in the second paroxysm of Chart 42, and thus simulate a quotidian fever.

In severe cases the fever may be of a remittent type for several days, the temperature remaining continuously above normal, but *the longest period I have seen a fever showing malarial parasites in the blood, under efficient quinine treatment, is six days*, as illustrated

FEVERS IN THE TROPICS

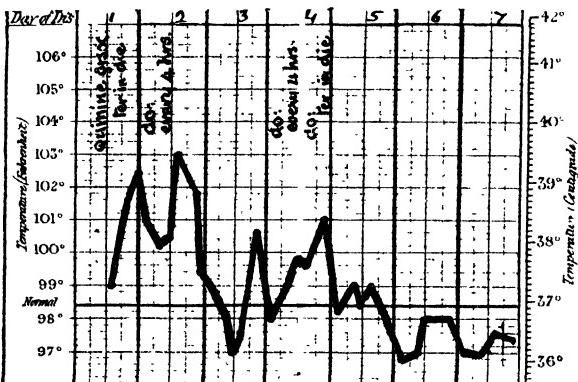
by Chart 43. This is a point of the greatest practical importance in India, where the great resemblance of kala-azar and other long fevers to malaria formerly led many, including myself, to look on some remittent fevers, which resisted quinine for many days, as

CHART 41 (Case 123)



Malignant tertian malaria showing a steady decline in the height of the paroxysms under quinine treatment.

CHART 42 (Case 780)



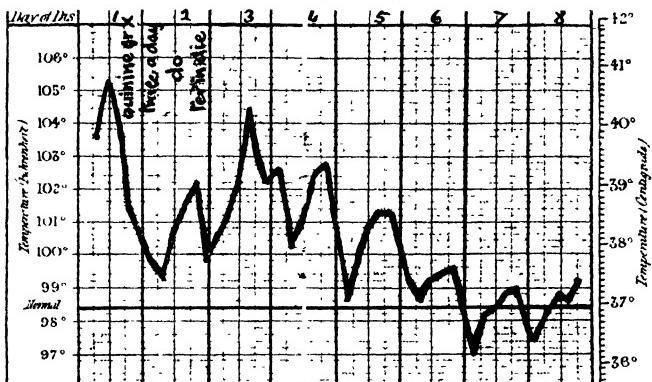
Malignant tertian malaria with well-marked remissions during the pyrexia, which reached the normal in the last paroxysm simulating a quotidian type.

still possibly malarial in nature. This I am now convinced is a serious error, for no such case with malarial parasites has been met with in two years' work among the 1350 consecutive fever cases in which I have microscopied the blood.

Quotidian Malignant Tertiaries.—Italian authors, followed by some English writers,

have described quotidian malignant tertian fevers with a daily rise of temperature, and even state that there are two varieties of the disease in accordance with whether the small

CHART 43 (Case 92)



Malignant tertian malaria, showing a severe infection with remittent fever, and lasting six days under quinine treatment, the longest duration met with.

CHART 45 (Case 767)

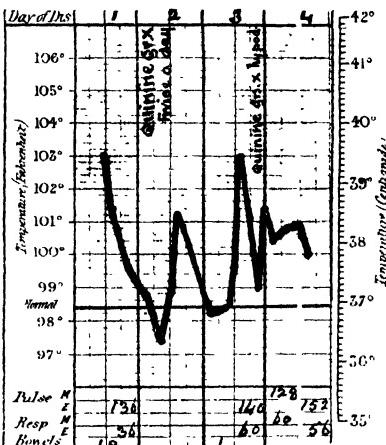
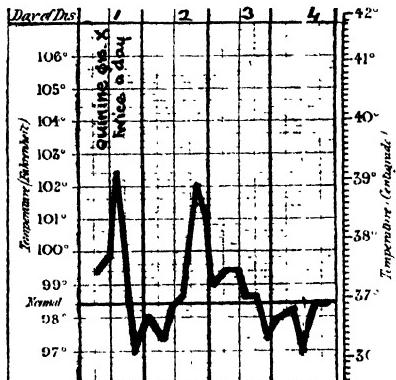


CHART 44 (Case 153)



Malignant tertian malaria, showing an apparently quotidian type probably due to shortening of the paroxysms under quinine.

Temperature curve in a fatal irregular malignant tertian malaria, whose true cause was not recognized until numerous rings and crescents were found by a routine blood examination.

ring parasites are or are not pigmented. On the other hand, we have the high authority of Koch for saying that only one malignant form of malaria is known, whose curve usually presents the character described above, but which may occasionally present shorter

paroxysms, and thus assume a quotidian appearance. I have carefully watched for such quotidian cases, but they have been very rare in my experience in India. Among over 100 cases showing the small malignant tertian parasites I have only two charts showing a quotidian type of fever for two and three days respectively in each case; one of these is shown in Chart 44, the paroxysm being of only from twelve to sixteen hours, although very numerous malignant tertian parasites were found. The other case is a doubtful one, as the chart of the first paroxysm is incomplete, and the second one, which followed after an aipyrexial interval of sixteen hours, lasted only twenty hours, but may have been an abortive one. I could not find any differences in the parasites of these cases and those of typical malignant tertians, while it appears to me that they may possibly be explained as being due to an exaggeration of the usually slight remission at the height of the temperature curve of typical cases, such as the second paroxysm in Chart 42, already referred to. Whatever may be the case in Italy, and perhaps in Africa, I am of the opinion that there is not as yet sufficient evidence of the existence of a separate quotidian malaria in the East, and nothing is to be gained by subdividing the malignant tertian fevers without further proof of undoubted distinctions between the clinical course and the parasites of this type. Irregular forms such as the fatal case shown in Chart 45 are sometimes met with and may occasion great difficulty, this case having only been recognized through the routine examination of the blood.

The Duration of the Paroxysm in Malignant Tertian Malaria.—*As the prolonged rise of temperature is so characteristic of malignant tertian fever, and the most distinguishing clinical point between it and the benign forms, it is of importance to know how constantly the disease shows this feature.* In analysing my cases for this purpose those in which no complete paroxysm took place after admission to hospital, as well as the low intermittents (still to be mentioned), have had to be excluded. Of the remaining cases four-fifths showed the pyrexia lasted for twenty-four hours or more, while in most of them it was of over twenty-eight hours' duration. In half the exceptions the duration was between twenty and twenty-four hours, so that in only 10 per cent was it under twenty hours, and in some of these quinine had been taken before the commencement of the rise, which probably shortened its duration. It is clear from this that a pyrexia of twenty-four or more hours' duration is met with in the vast majority of malignant tertian paroxysms, which as we shall see serves at once to distinguish this form from the great number of benign tertians and quartans.

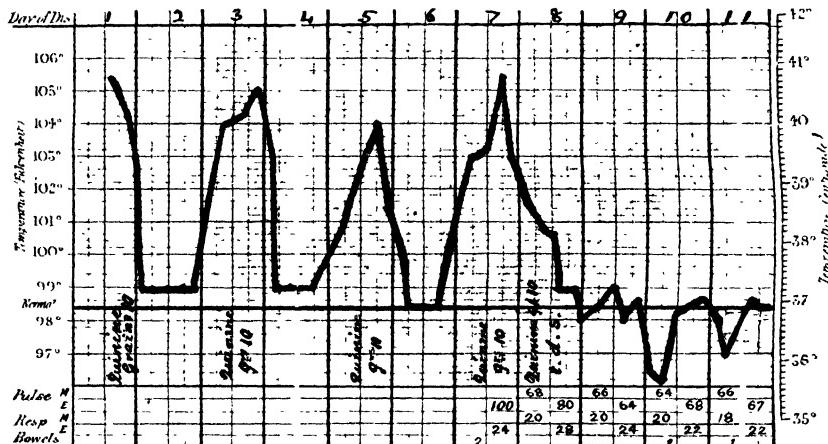
Low Intermittent Fever in Malignant Tertiaries.—One more variation from the normal type remains to be considered. In nearly 10 per cent of my malignant tertians a low intermittent form of pyrexia, rising to only about 100° F., occurred, in more than half of which crescents in larger or smaller numbers were found together with a variable, but usually small, number of rings. These cases are important because they are very liable to be overlooked and sufficiently prolonged quinine treatment neglected. Thus, in one case illustrated in Chart 45, the true cause of the fever was not suspected until I reported finding crescents in the blood several days after admission, up to which time no quinine had been given. The case terminated fatally two days later in spite of the drug being then commenced.

Recrudescences and Relapses.—This leads to the question of relapses. It has been noted by several workers in India, and especially by A. Buchanan, I.M.S., at Nagpur, that there is a marked tendency in malignant tertians for the fever to recrudesce about eight days after the temperature has fallen to normal, and that this reappearance of the fever is accompanied by the presence of crescents as well as rings in the blood. This takes place chiefly in patients who have not continued to take full doses of quinine after the cessation of the primary fever. The low fever just described may occur during this quiescent period. Moreover, true relapses, as opposed to the recrudescences after a short interval, may occur for a long period after the first attack, although in India they appear to be less frequent in malignant than in the benign forms of malaria. Norman Chevers suffered from typical malarial fever with ague for thirty years after infection in Chittagong, and long after his return to England. Prolonged use of quinine in prophylactic doses as already advised is necessary to prevent relapses, and for this reason it is essential to make a microscopical examination of the blood in all doubtful fevers which may possibly be malarial.

THE TEMPERATURE CURVE IN BENIGN TERTIANS

The classical curve of a benign tertian malaria is a rise of temperature every other day as in the single infection shown in Chart 43. Among Europeans in India, however,

CHART 46 (Case 1438)

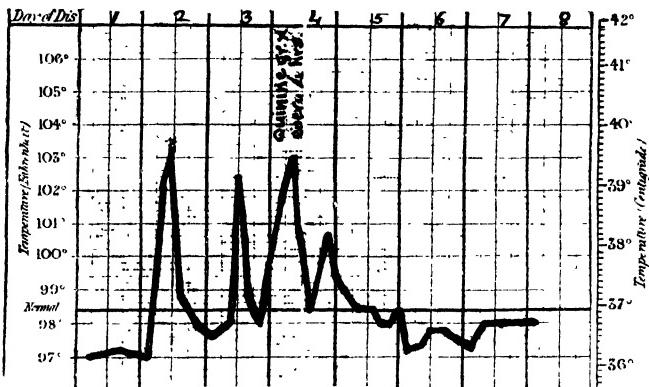


Typical single benign tertian malaria uninfluenced by 10-grain doses of quinine every other day, but yielding rapidly to 30 grains daily.

this form is much rarer than the less typical double infection producing daily paroxysms of fever. Chart 46 shows a pyrexial rise every other day for four paroxysms, which could not well be produced by anything except a single benign tertian infection, but such a chart is never seen in patients who are treated with full doses of quinine immediately they come under observation. This patient had only 10 grains every other day up to his

admission on the eleventh, and as soon as he was given 30 grains a day the fever ceased after one day. The height to which the temperature rose in this chart is also noteworthy.

CHART 47 (Case 6)

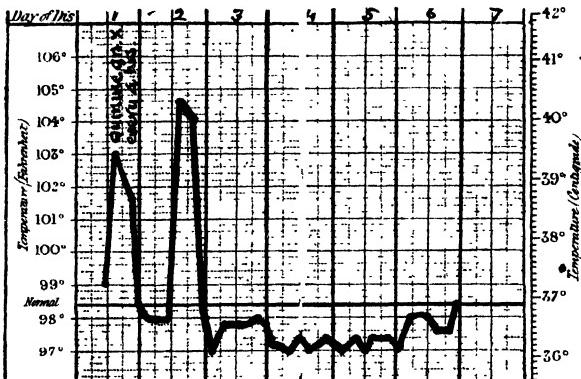


Typical double benign tertian malaria yielding rapidly to 60 grains.

105° F. or over having been reached in three of the four attacks : a very common occurrence in benign tertians, but much rarer in malignant ones.

Double benign tertians are illustrated in Charts 47 and 48, the first showing three paroxysms in a patient attacked while in hospital, and the second, two in as many days.

CHART 48 (Case 34)

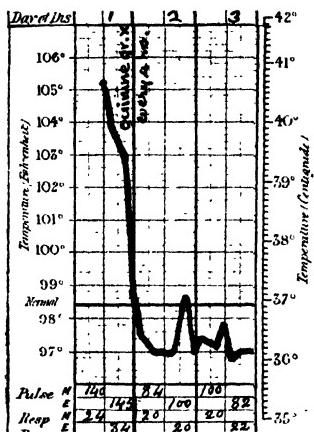


Double benign tertian malaria yielding in two days to quinine.

Note that the temperature remains raised for only from eight to sixteen or, more rarely, twenty hours, in marked contrast to the much longer duration in malignant tertians as already illustrated. In a place where malaria is prevalent a fever which rises very rapidly

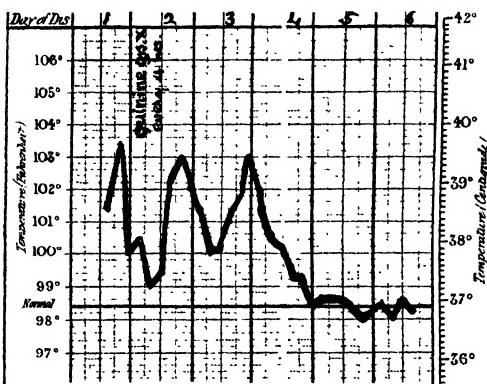
to 105° or 106° with a rigor, and falls again in a few hours to normal or subnormal, is nearly always a benign tertian malaria, especially if the patient appears to be quite well and able to go about his work in the apyretic intervals; this would be impossible, if suffering from any septic or inflammatory condition producing such severe daily fever with rigors. Chart 49 also shows a very high temperature, with a quick pulse, falling rapidly to subnormal. It is a benign tertian case, admitted during a paroxysm of fever, in which prompt quinine treatment prevented any further ague fit. So rapid is the effect of full doses of quinine in cutting short the attacks of this fever, that one-fourth of my benign tertians showed either, only such a partial paroxysm, or no fever at all, after admission to hospital. Another fourth showed the daily rises of a double infection, while 12 per cent gave a history of a single infection with fever every other day.

CHART 49 (Case 252)



Benign tertian malaria, showing only the end of one paroxysm under 60 grains of quinine daily.

CHART 50 (Case 8)



Severe benign tertian malaria with remittent fever.

Only 6 per cent actually showed the typical single tertian temperature curve in hospital, although probably a fair number of those which were cut short by quinine after a single paroxysm might have been single infections. Microscopically, too, infections showing the parasites in all stages of development were by far the commonest, so that it is clear that a double infection is the general rule, and typical single tertian charts are quite exceptional. The general belief in India up to a recent time that benign tertian malaria was very much less common than the malignant form no doubt arose in consequence of the rarity with which the classical charts of text-books were met with in practice, and it is only since the more general use of the microscope in fevers that the great frequency of benign tertians, and also the less rarity of quartans than was formerly supposed, have been ascertained in India. In some cases of the common double tertians the rise of temperature may be higher on the odd than on the even days, due to one infection being more numerous than the other. This may sometimes be of diagnostic value,

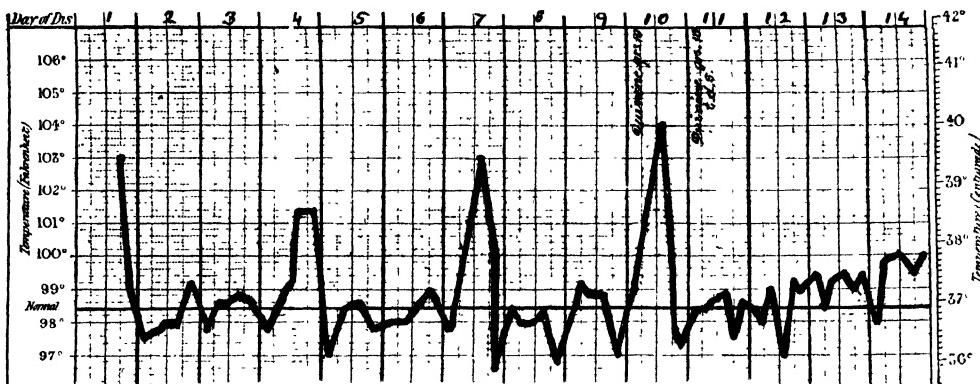
but as a rule the fever does not last long enough under treatment to allow of its being seen.

Benign tertians very rarely show a remittent temperature curve, the normal line being almost always reached between the paroxysms. Chart 50 is of interest as showing the most remittent case I have met with in a benign tertian infection. One fatal case occurred among the 99 in this series. Occasionally a paroxysm may show an irregular prolonged temperature curve lasting over twenty-four hours, usually in severe infections with very numerous parasites.

THE TEMPERATURE CURVE IN QUARTANS

Quartan fevers are much rarer than the other forms in all parts of India where the question has yet been investigated, except in North-Eastern Bengal, although they were found by the Malaria Commission to be fairly common in the intensely malarious sub-Himalayan Duars, and I myself have seen them frequently in children in a very malarious part of the Nowgong district of Assam. Among my European series I only met with 5 cases out of 200 malarial fevers in two years, and in only one of these was the classical text-book chart obtained, the patient having been admitted for phthisis and only examined for malaria on account of his showing fever every third day as in Chart 51. The other

CHART 51 (Case 1092)

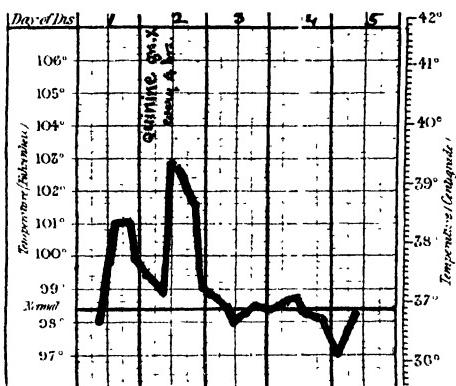


Typical single quartan malaria, yielding at once to 50 grams of quinine daily.

cases were all double infections, or possibly some of them triple ones in which the fever was cut short after two paroxysms by quinine. Chart 52 shows the usual double type met with, but which would not have sufficed to allow of a correct diagnosis being arrived at without the microscopical examination showing the quartan parasites. A. Crombie's statement that he had seen only two quartan fevers in his many years' service in Bengal was doubtless based on clinical evidence, but he overlooked the most common double type of infection. Dr. Upendranath Bramacheri recorded 5 quartan cases at the Medical College Hospital, while Megaw's series include 37 quartans, only 7 of which had probably

been infected in Calcutta itself, and the rest in Lower Bengal districts. Out of 25 charts, 13 showed typical single quartan ague, this form being much more common in native than in European patients. The probable explanation of this is that Europeans come earlier under observation with double or triple infections, but that in the chronic cases seen in natives one or more of the infections have died out, leaving a single one. The duration of the paroxysms is also only a few hours in the quartans, just as in the benign tertian form, but the pyrexia less frequently reaches an extreme height in quartans, these being

CHART 52 (Case 491)



Double quartan malaria yielding in two days to 60 grains of quinine daily

the mildest of the three types; on the other hand, they show the greatest tendency to relapse in spite of the paroxysms being very rapidly cut short by quinine treatment. This clinical fact indeed often leads to too early cessation of the drug and consequent recurrences.

DURATION OF FEVER AFTER TAKING QUININE

Reference has already been made to the rapidity with which malarial fevers are often cut short by quinine, but the very important question as to the limits of their duration under proper treatment remains to be considered. In the European series quinine was given in doses varying from 20 to 60 grains in the twenty-four hours, the larger quantity being most commonly employed, and next most frequently 30 grains. The dose was nearly always 10 grains, which was administered from two to six times in the day. The duration of the fever in hospital under these different quantities of quinine has been worked out for both the malignant and benign tertian cases with instructive results. In the first place there was no appreciable difference in the duration of either type of fever whether 20, 30 or 60 grains of the drug were administered daily, so that the largest dose named is clearly unnecessarily great; it gives rise to a good deal of deafness and buzzing in the ears, although apparently less in truly malarial than in other fevers. On the whole, I think 30 grains daily is the right quantity for adult males, while 20 may perhaps

be enough in women, who ordinarily weigh considerably less than men, and are more sensitive to the unpleasant effects of the medicine. Table XXXII. shows the number of

TABLE XXXII.—DURATION OF FEVER AFTER TAKING QUININE

	Malignant Tertians. Amount of Quinine Daily.			Benign Tertians. Amount of Quinine Daily.			Total.	Per- centage.
	60 Grains.	30-40 Grains.	20 or less.	60 Grains.	30-40 Grains.	20 or less.		
No fever . . .	0	4	3	4	4	3	18	9·7
One day . . .	15	11	2	14	14	8	64	34·9
Two days . . .	10	9	4	13	9	2	47	25·6
Three „ „ „	10	8	6	5	4	2	35	19·1
Four „ „ „	6	1	1	2	2	1	13	7·0
Five „ „ „	..	3	1	4	2·1
Six „ „ „	2	..	1	3	1·6
Average total cases . . .	43	36	18	38	33	16		
Average duration	2·35	1·7	2·4	1·6	1·67	1·44		
Average duration total cases . . .		2·1			1·57			

Note.—Most of the patients treated with 20 grains or less were children.

days the fever lasted under varying doses of quinine. The average duration of the whole of the malignant tertian cases was only 2·1 days, and of the benign tertians it was only 1·57 days, a remarkable testimony to the specific action of quinine against malaria. Of still more practical importance is the fact that no case of benign tertian fever lasted more than four days under this treatment, while no malignant tertian persisted more than six days (see Chart 43, p. 245). Moreover, only 8 per cent of the malignant tertians lasted more than four days, and in none of these did the fever remain of the remittent type without falling to normal for over four days. These striking facts clearly establish that the malarial fevers of Lower Bengal, and presumably of other parts of India, are not more persistent under adequate quinine treatment than are those of Europe and America, where similar evidence has long since been forthcoming. Stott, however, at Mandalay, Burma, met with a very few malarial cases in which the fever lasted slightly longer than six days under quinine.

It may therefore be laid down as an axiom that any fever which lasts longer than the time limits stated under proper doses of quinine is not malarial, or at least not purely malarial in nature. It is, however, essential to know that the drug is really being taken in adequate doses and in an assimilable form. Thus, after I had come to the conclusion just stated it was brought to my notice that in several cases showing malarial parasites in their blood the fever had persisted in a native hospital for over the periods laid down, and that, too, in spite of 30 grains of quinine being ordered to be given daily in acid solu-

tion. On my suggestion the quinine solution supplied from the dispensary was analysed and found to contain only 4 grains to the ounce instead of 10. In India, where so much has to be left to very poorly paid subordinates, the temptation to make away with such a readily saleable drug is very great, and requires special watchfulness.

Type of Anaemia in Malaria.—As a result of repeated attacks of ague much deterioration of the blood rapidly takes place, producing clinically evident anaemia. This is of the pernicious type, the reduction in number of the red corpuscles being equal to or greater than that of the haemoglobin, so that the colour index, or percentage of haemoglobin in the corpuscles, is normal or slightly in excess. This type is, however, also met with in kala-azar, but in that disease, except in the very late stages, the degree of anaemia is less marked than in true chronic malaria. The occurrence of the pernicious type of anaemia is doubtless due to the fact that as the red corpuscles are destroyed within the body, such of the haemoglobin as has not been converted into malarial pigment is stored up in the liver and spleen, and so can be utilized in stocking new red corpuscles as they are produced by the red marrow, and so the proportion of haemoglobin in the corpuscles remains high. For this reason arsenic and red marrow tabloids, to increase the output of red corpuscles, are of more value in malarial anaemia than iron, and once the destruction of the blood is stopped by killing off the parasites with quinine, rapid improvement follows from this line of treatment. For example, in two chronic malarial cases in sailors from Mauritius the red corpuscles increased from $1\frac{1}{2}$ and $2\frac{1}{4}$ millions respectively to 4 and $3\frac{3}{4}$ millions in one month.

The White Corpuscles in Malaria.—In addition to the occasional pigmentation of the white corpuscles already referred to, marked variations from the normal occur both in the total numbers and in the proportions of the different varieties. Except in rare cases of exceedingly acute infections, the leucocytes are diminished in numbers. When an extraordinary number of parasites are present there may be an increase in the leucocytes amounting to an actual leucocytosis, as in a case recorded by T. H. Delaney, I.M.S., in which 23,000 leucocytes per cubic millimetre were found. The leucopaenia seen in the great majority of cases varies considerably in degree, being most marked in cases of malarial cachexia following repeated attacks. Of 19 consecutive cases examined by me in Nowgong, including all three varieties of malaria, in 7 the white corpuscles were within the normal limits of from 6000 to 10,000; in 10 more they numbered between 4000 and 6000; and in the remaining 2 they were 2625 and 3520 respectively. Thus the degree of leucopaenia is seldom very marked, and does not approach in severity to the reduction which is practically always found in uncomplicated kala-azar in its typical stages. A further and more characteristic distinction between the two diseases is found when the proportion of white to red corpuscles is worked out, for in none of the 19 cases of malarial cachexia did the ratio fall to as low as 1 white to 1000 red, in spite of the marked leucopaenia in two of the cases, although I have rarely met with slightly greater reduction. On the other hand, I have shown in Chapter III. that in typical uncomplicated cases of kala-azar the ratio is almost always below 1 to 1500, and frequently much lower than that figure. In fact, I look on this great reduction of the white corpuscles

relatively to the red as practically diagnostic of kala-azar as against true malarial cachexia, and have found this point to be of great clinical value.

The Differential Leucocyte Count in Malaria.—An increase of the proportions of the large mononuclear leucocytes has been found by a number of observers to occur very frequently in malaria. Its incidence has been carefully studied by Stephens and Christophers in their reports to the Royal Society from West Africa. They showed that it may be absent or only slight in degree during pyrexia, although well marked in the same cases in the intervals from actual fever, and they regarded over 15 per cent of large mononuclears as proof of an actual or recent malarial infection, and of over 20 per cent as implying actual infection at the time. This statement is probably correct with regard to the general run of fever cases in West Africa, but many hundreds of blood counts I have made in all kinds of fevers in India show that equally high percentages of large mononuclears may be met with in two other fevers besides malaria, namely, kala-azar and seven-day fever. The frequency of different degrees of the increase in both malignant and benign tertians in relationship to the temperatures worked out from counts in every case in my European series for one complete year is shown in Table XXXIII., which may be compared with similar tables for the other two fevers mentioned on pages 41 and 304.

TABLE XXXIII.—LARGE MONONUCLEAR INCREASE IN MALARIA

Temperature.	Malignant Tertians			Benign Tertians			Total.			Percentage.	
	-100	100-102	+102	-100	100	+102	-100	100	+102	Author's Cases.	Stott's Cases.
0-8 per cent	4	..	1	1	6	77	86		
8-12 "	3	..	4	..	2	1	10	130	129		
12-15 "	6	5	3	5	5	1	25	325	123		
15-20 "	2	3	1	6	3	1	16	207	190		
Over 20 "	1	5	3	6	4	1	20	260	472		

There are several points of interest to be noted in these figures. In the first place they confirm the general rule of Stephens and Christophers that the increase of the large mononuclears is less marked during high fever than when the temperature is normal, and further show that this change is in proportion to the height of the temperature when the blood is taken. Secondly, the increase is distinctly more marked and frequent in benign than in malignant tertians, the much shorter duration of the febrile paroxysm in the former leading to the blood film being much more frequently made when the temperature is normal than in the case of the malignant tertian, in which the apyretic intervals are so very short. This is so definite that whenever I note a very marked increase of the large mononuclears in the first rapid survey of a blood film from a case which is likely to be malarial with an $\frac{1}{8}$ -in. lens, I immediately seek for the large benign tertian parasites along the edge of the specimen with the same power, and often find them within a few seconds.

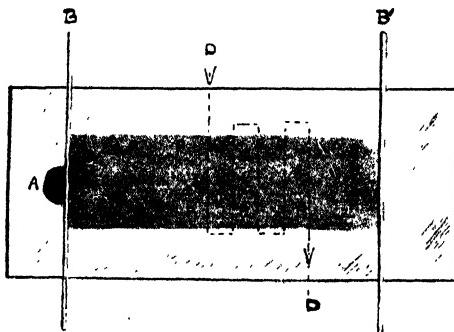
When we come to consider this change as a diagnostic measure, however, we find that over 15 per cent of large mononuclear leucocytes were found in only two-fifths of the malignant tertians and in three-fifths of the benign form, or just under one-half of the total cases. In no case was a normal count of not over 8 per cent met with during an aipyrexial period, but in a large proportion intermediate numbers between 8 and 15 per cent were found. Stott has also studied this change in Burma, and his figures are given at the end of Table XXXIII., and show a larger proportion of counts exceeding 15 per cent, namely, 66 per cent. In twenty-five healthy Indians he only found such a high count in 8 per cent, so regards it of considerable diagnostic value if done by a reliable observer whose personal equation is known.

When we come to compare these figures with those for kala-azar, we find that in the European series of the latter disease dealt with on page 41, 35 per cent gave counts of over 15 per cent of large mononuclears, although they include a number of early cases. Further, among twenty consecutive advanced cases in Assam no less than 62 per cent gave similar counts. In fact, before the discovery of the parasite of the disease I advanced this fact in favour of kala-azar being malarial in origin. Again, in the case of seven-day fever no less than 20 per cent gave these high large mononuclear counts. It is clear from these data that this test is of very little value in the diagnosis of malaria in tropical countries in which these other fevers commonly occur, and although the estimation is more troublesome than searching for malaria parasites, it is only in exceptional cases that the increase of the large mononuclears has any value, and much caution is required in its use. On the other hand, an increase of these leucocytes is of great value in excluding typhoid fever in the first two weeks of that disease (see p. 131).

The Arneth count of the proportions of polynuclear leucocytes with from one to five lobes of the nucleus has been found by Knapp in Burma and Macfie in West Africa to show a marked shift to the left in malaria. Macfie found a slight shift to the left in healthy Europeans, who had, however, mostly suffered from malaria, which he thinks accounts for it. In actual malarial cases he found Arneth's index, namely, the percentage of polynuclears with only one or two lobules to the nucleus, averaged 86·6 against a normal of 40, while the limits were from 7·1 and 97·5. In yellow fever he found a similar and equally marked change.

Examination of the Blood for Malarial Parasites : Preparation of Blood Films.— For all blood examinations of stained specimens smears on slides are preferable to cover-glass preparations as furnishing the larger amount of material which is often necessary. They may be prepared by placing a small drop of blood, obtained by pricking a cleansed finger or lobe of an ear, near one end of the glass slide, and laying either the end of another slide with its surface at an acute angle to the first, or a long needle, as recommended by Stephens and Christophers, across the drop of blood and gliding it along towards the other end of the slide, producing a smear extending from half to two-thirds of the breadth and length of the glass as shown in the Illustration below. The drop of blood should be sufficiently small to fray out into points and be exhausted before the end of the slide is reached. If a second piece of glass is used to spread out the blood the more acute the angle between it and the slide on which the smear is being made, the thinner will be the resulting

blood film. It is better to take too small a drop than too large a one, for in the latter case little or none of the film may show all the red corpuscles properly separated from each other. This result it is so desirable to obtain when looking for malarial parasites.



A, spot of blood placed on slide. B, needle placed across drop of blood and drawn across to B.
C, parts of film where lymphocytes are in excess.
E, parts of film where polynuclear, large mononuclear and eosinophiles are most numerous.
D—D, line of count across slide.

Methods of preparing blood films, and the distribution of the various kinds of leucocytes in them.

Unless a combined fixing and staining reagent is used, the film must next be placed in either equal parts of absolute alcohol and ether, or the former alone, for ten minutes to fix the blood. If absolute alcohol is not available methylated spirit can be used for this purpose. Exposure for a few seconds to the fumes of a 2 per cent solution of osmic acid also fixes blood well.

For **staining** Romanosky's method, or one of its numerous modifications, is the most generally useful one for blood examinations, as it stains equally well bacteria, the parasites of malaria, kala-azar or filarial disease, and also the different forms of leucocytes. The original method has the disadvantage of requiring preliminary fixing and taking longer for full staining than some of its later modifications. The most convenient of these is that of Leishman, in which the specially prepared stain is dissolved in pure methyl alcohol (Merck's), so that it can be used for both fixing and staining the film in the following manner: Some four or five drops of the fluid are poured on to the slide from a drop bottle so as completely to cover the blood smear, and left in contact for from fifteen to thirty seconds to fix it, strong currents of air, which will rapidly evaporate the alcohol and precipitate the stain, being guarded against. About twice as many drops of distilled water (any clean water usually does equally well) are then added and produce a fine precipitate of the active principle of the reagent, which stains the film in from three to ten minutes or more in accordance with the strength of the original solution. Personally I prefer to use it sufficiently strong to stain malarial parasites and leucocytes well within five minutes, as it then becomes an eminently useful clinical method for employment in the microscopical room, which should be a feature of all hospitals in the tropics. The slide is now washed in a current of water under a tap or from a wash bottle to remove the staining fluid (this

process not being continued for long unless it be overstained, as it soon begins to decolorize the film), and then dried without the application of heat, which may also injure the result.

If the original Romanosky method is used the two dilute solutions of eosin and medicinal methylene-blue are simultaneously poured on the slides in equal quantities, about half to one hour being required to obtain deep staining. It is a good plan to place the previously fixed slides face downwards with one end slightly raised by a match, as this prevents precipitation on the film which sometimes obscures the result. Giemsa's stain also produces very beautiful results, which are worth the extra time and cost when specimens for demonstration are required, but it is an unnecessary luxury for ordinary clinical work.

As there may often be difficulty in obtaining Merck's methyl alcohol in remote tropical places, the following method of using in its place ordinary methylated spirit for dissolving Leishman's stain as recommended by F. Tulloch, R.A.M.C., may sometimes be of value : To 25 c.c. (7 fluid drachms) of methylated spirit add exactly two drops of a 10 per cent solution of potassium bicarbonate. In this alkaline spirit make a saturated solution by grinding a slight excess of the powdered stain in a pestle and mortar, and bottle it. Fix the blood film in equal parts of methylated spirit and ether for ten minutes, dry and stain as with ordinary Leishman's solution for five to eight minutes. Wash in distilled water for thirty seconds, and then in 1 in 1500 acetic acid for a few seconds until the film becomes of a bright eosin pink, rinse in distilled water and dry.

Ross's Thick-Film Process may sometimes be of use, especially in searching for filaria, and occasionally in looking for malarial parasites when they are very scanty. The blood is spread out in a much thicker layer than usual, so that the red corpuscles lie over each other. After drying, a few drops of water are gently poured on the slide and allowed to remain for a few minutes until all the haemoglobin is dissolved out, and then carefully run off. After allowing to dry again, the film is fixed and stained by one of the methods already described. Such organisms as filaria can then be readily seen through the decolorized red corpuscles, while the blue rings with the reddish chromatin bodies of malarial parasites may also be similarly visible, and owing to the concentration of the blood a much larger quantity can be searched for them in a given time than in an ordinary thin slide. I have not, however, found this method to work well in the case of the parasites of kala-azar, which are quickly damaged by the action of distilled water.

Another method of preparing a thick blood film, which I have found of more general value, is first to fix and stain with one of the Romanosky modifications, and then rapidly to dissolve out the haemoglobin from the superimposed red corpuscles by a very dilute solution of acetic acid, which does not at once decolorize the parasites of malaria, kala-azar, etc. In this way the outlines of the red corpuscles remain distinct, and the relationship of the parasites to them can be clearly distinguished although they have become transparent.

W. M. James's modification of Ross's thick-film method has also been recommended by several workers, and may be carried out in the following way : A fairly large drop of blood is spread in a circle of about three-quarters of an inch in diameter and allowed to dry. Immerse in a mixture of ten drops of strong hydrochloric acid in 50 c.c. of ethyl

alcohol until the haemoglobin has been dissolved out. Wash in running tap-water for ten to twenty minutes, or according to Bosco time may be saved by placing the slide in weak bicarbonate of soda to neutralize the acid instead of in running water. Dry and stain with undiluted Romanosky for two or three minutes, and then dilute freely, carrying out this dilution in successive stages for about ten minutes, and finally wash in tap-water until no more blue colour comes out of the film. Taylor compared the thin- and thick-film methods in 3613 apparently healthy persons in the Southern States of America, and found malarial parasites in 526 thick films in examinations of five minutes' duration, but in the corresponding 526 thin films which he examined for thirty minutes he only demonstrated them in 125 cases : clearly showing the great advantages of the thick films.

Methods of concentrating Malarial Parasites for Diagnostic Purposes.—Bass and Johns have elaborated a method for concentrating the parasites by means of the centrifuge, based on the fact that the plasmodium containing red corpuscles, except those with only small ring forms, are enlarged and are found concentrated at the top of the column of red corpuscles, and below the leucocytes. To 10 c.c. of freshly drawn blood add 0·2 c.c. of 50 per cent solution of dextrose to prevent changes in the parasites. Defibrinate or add 0·2 c.c. of a 50 per cent solution of sodium citrate, preferably the former. Centrifuge at a speed of from 2000 to 2500 revolutions per minute in tubes of 1·5 cm. inside diameter for one minute for each cm. depth of blood in the tube, which should contain 2 to 5 cm.. until the cells are completely separated from the plasma and the leucocytes in the surface layer, when the parasites will have risen with the leucocytes, and be contained in the upper 0·1 cm. Take up the leucocyte layers with a fine pipette and centrifuge it again in a fine smaller tube, and make films from the leucocyte layer of this second centrifuged column. It is claimed that in the best preparations the parasites are concentrated about 900 times, and that as many parasites should be seen in one minute as in fifteen hours' examination of the same blood in ordinary films. Where good laboratory accommodation is available this method should be of great value in doubtful cases of malaria.

THE DIFFERENTIAL DIAGNOSIS OF MALARIAL FEVERS

It has been shown that both the actual presence of malaria and the actual type of the fever can readily be detected by the characteristic temperature curves which have been described, when they are available. However, the classical text-book charts are seldom seen in practice owing to the duration of malarial fevers only averaging two days under quinine, for this is usually given to every fever patient immediately on coming under observation. To withhold the drug until the nature of the disease has been verified by the occurrence of the typical chart or by microscopical examination is impracticable and unjustifiable under ordinary conditions of work in the tropics with the large number of fever cases which come daily under treatment. To do so in really malarial places would sooner or later lead to preventable deaths taking place. The plan, already mentioned, of always making a blood slide immediately on admission, before the first dose of quinine is administered, gets over this difficulty, as it can subsequently be examined at leisure in every case which is not clearly malarial clinically, yet may possibly be of

this nature. It is only in this way that all the malarial cases can be separated out from other fevers in the tropics. It is obvious that this is of vast importance in order that malarial cases should be efficiently treated by a prolonged course of quinine.

Nevertheless it may be of service to repeat here the points of greatest practical value in the clinical differentiation of malaria from those fevers with which it is most often confused.

1. From Fevers of Long Duration such as Kala-azar, Typhoid and Malta Fever.—Now that the bugbear of fevers in the East has been removed by the separation of kala-azar from true malarial cachexia, and it is clear that there is no such thing as a malarial fever which resists adequate doses of quinine for many days or weeks, the differentiation of malaria from typhoid, Malta fever and kala-azar in their active phases is quite simple, for a few days' record of the temperature curve, while quinine is being administered, will allow of malaria being excluded. Moreover, the high continued type, described on page 105 as being so characteristic and frequent in typhoid, does not occur in malaria, while the double remittent type of the early stages of kala-azar is equally rare, if indeed it occurs at all, in malarial fevers. The charts of Malta fever are less characteristic and the duration and undulating character of the pyrexia will here be the best guide.

2. From Fevers of Short Duration such as Seven-Day Fever, Influenza, Dengue, etc.—When we turn to the clinical differentiation of malaria from other fevers of short duration the problem is more difficult. In large tropical seaports, such as Calcutta, the fever which is most frequently confused with malaria is the seven-day fever described on page 294. When the patient is admitted in an early stage of the disease the saddle-back temperature curve and the ineffectiveness of quinine will soon exclude malaria, especially when the pyrexia is of a fairly continued type such as Chart 73 on page 331, which is never seen in malaria. The frequent cases, however, which are admitted during the terminal rise of temperature (see Chart 78, page 351) and fall in a day or two while taking quinine may readily be mistaken for a single paroxysm of malignant tertian malaria. This mistake may be avoided in the great majority of cases by noting the pulse rate when the temperature is up to 103° or more, for I have scarcely ever seen it over 100 a minute in this terminal stage of the seven-day fever with such a degree of pyrexia, while it is nearly always over 100 a minute in a malarial case under such conditions. The greater severity of the pains in the back and limbs and of the frontal headache as well as the red raw edge to the tongue also point to seven-day fever rather than malaria.

Influenza may sometimes present difficulties, but as a rule the presence of sore throat, coryza and physical signs of bronchitis, etc., in the lungs will indicate the true nature of the disease, for they are very rarely met with in malaria. Further, influenza in India occurs usually in the early months of the year in the cold season, during the minimum prevalence of malaria. The three-day fever described by McCarrison in Chitral, which occurs in the hot weather in the United Provinces and Punjab, as described on page 308, has also been frequently mistaken for malaria, but it shows a different temperature curve. Dengue usually occurs in the tropics at long intervals in an epidemic form of such wide and rapid distribution and with such a marked rash that it is readily recognized. Should

it occur at any time in a sporadic form the remittent or intermittent temperature curve might well lead to its being mistaken for malaria, but the intense break-bone pains and absence of malarial parasites should lead to its recognition.

The cerebral type of malaria may be mistaken for a variety of conditions which have already been mentioned. Only a microscopical examination of the blood will enable these to be differentiated.

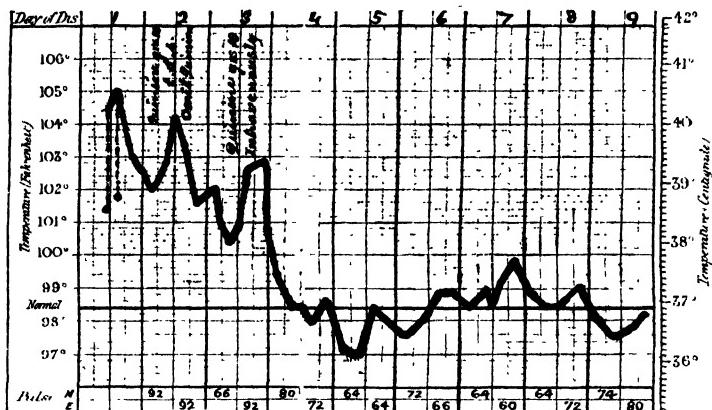
COMPLICATIONS OF MALARIA

Cerebral Malaria.—By far the most serious and important complication of malaria is the condition of coma brought about by blocking up of the capillaries of the brain by innumerable parasite-laden red corpuscles. It only occurs in very intense infections, as in the case already mentioned from which the later stages of the malignant tertian parasites of the coloured plate were drawn. The importance of always bearing this condition in mind is that these cases are sometimes erroneously diagnosed as heatstroke, cerebral haemorrhage, or even as plague—as in one patient whom I rescued from the plague ward while engaged in a research on the blood changes in that disease; again another case seen in consultation had been treated as plague until a hopeless comatose stage was reached. Now during this complication of malaria (which by the way is almost always of the malignant tertian form) the parasites are so numerous in the peripheral blood that they are seen in every field of the microscope, so they can be found easily within five minutes, including staining the slide. They mostly occur at the height of the malarial season, although grave cases may be met with at any time of the year, so that in all cases of coma in the tropics, not obviously due to injury or other cerebral disease, the examination of the blood for malarial parasites should be at once undertaken.

Unfortunately, once coma has become established in an adult patient it is generally too late to save the patient's life, although in children better results are sometimes obtained. Further, this form of malarial coma may set in very suddenly in cases which do not appear clinically to be unusually severe infections, although they are readily found to be so by the briefest microscopical examination of the blood. For example, a native patient in whose blood numerous malarial parasites had been found in every field of the microscope showed no dangerous symptoms up to midnight, yet, in spite of 20 grains of quinine by the mouth, he became comatose in the early morning hours and was dead by 8 A.M., his brain and other organs being found choked with malarial organisms. Since that experience I have always administered quinine intravenously in patients showing such very large numbers of parasites in the blood, and the occasional occurrence of such cases is the very strongest argument for even a short examination of the blood in every fever case immediately on coming under observation in malarious countries. Chart 53 is that of a case in point, the patient having been admitted on June 10 with a high remittent fever, which was considered clinically on the 11th by both Dr. J. G. Murray (under whose care he was) and myself to be typhoid. When examining a blood slide taken in a routine manner for my investigation on the morning of the 12th, numerous malarial parasites were found in every field of the microscope. On visiting the hospital in the afternoon to report this, I learnt that his quinine had been omitted the day before on account of sickness and the temperature was rapidly rising again, so advised the immediate intravenous injection of

10 grains of the bi-hydrochlorate of quinine. As a result the temperature finally fell to normal the next morning, although it was just the kind of case which might have passed

CHART 53 (Case 1098)



Malignant tertian malaria, showing high remittent fever suspected to be typhoid. Very numerous parasites found by a routine blood examination; the fever yielded rapidly to an intravenous injection of 10 grains of bi-hydrochlorate of quinine.

into a fatal coma during the night if no more quinine had been given. In three cases of cerebral malaria with coma Megaw used intravenous injections of quinine without saving any of them, so that it is clear that the only way of being sure of avoiding such preventable deaths is to examine the blood of every fever case for parasites during the malarial season.

This case is also of interest as being the only malarial fever I have seen which could very well be mistaken for typhoid clinically, although some authors describe a typhoid-like variety of malaria.

Intestinal Malaria is a less common but important variety in which diarrhoea is the principal symptom, this being due to blocking of the intestinal capillaries by the parasites. A case admitted as cholera, but in which a routine blood count enabled me to recognize the true nature of the disease in time to save the patient, has been noted under the blood count in malaria. In another remarkable case the patient was admitted to my cholera ward in a collapsed and semi-conscious condition, but the low specific gravity of the blood led to a search for malarial parasites, with the result of finding no less than 47 malignant tertian organisms for every 100 red corpuscles, and vigorous treatment with 15-grain doses of quinine acid hydrobromide intravenously saved the patient's life.

Malarial Cachexia.—As a result of repeated attacks of malarial fever organic changes are produced in the system, which taken together constitute the clinical picture known as malarial cachexia. The most essential features of this condition are anaemia, some wasting, with enlargement of the spleen and often to a less extent of the liver. The degree of

anaemia in an Assam series of blood counts in children has already been treated of on page 250. It is commonly a marked clinical feature even in patients who have only suffered from malaria for a month or two, much more so, indeed, than in a similar stage of kala-azar which has for so long been confused with true malarial cachexia. The wasting, on the other hand, is much less marked in chronic malarial cases than in the more serious kala-azar.

The enlargement of the spleen is the most characteristic feature of malarial cachexia, especially in children, who have been shown to suffer so much from malarial infection. Thus in 19 Assam cases the organ reached to 4 in. below the ribs in 6, to the level of the navel in 8, and to below that level in 5. Yet these children were running about without apparent suffering, and many of them were fairly well nourished. Again, in a series of 30 patients in Dinajpur with great enlargement of the spleen, I found on spleen puncture malarial parasites in 5, those of kala-azar in 10, and neither organisms in the remaining 15. Clinically it was impossible at a single examination to distinguish between the chronic malarial and the sporadic kala-azar patients, so that it is not surprising that the two diseases have been confused for over a hundred years, or that in 1897 I could find no difference between the epidemic kala-azar cases and the sporadic ones known as malarial cachexia. They may, however, be nearly always microscopically differentiated by the approximately equal reduction of the red and white corpuscles in chronic malaria and the disproportionately great reduction of the white cells in kala-azar which has been described on pages 253 and 42.

The liver may also be considerably enlarged in malarial cachexia, but does not so often reach the extreme degree of extension as far as the level of the navel, as it does in the late stages of kala-azar. According to Kelsch and Kiener, malarial cirrhosis of the liver is not uncommon in Algeria, but their descriptions of "malarial cachexia" are very suggestive of kala-azar, which has been identified in the Sudan, and also found by Laveran in Tunis in Northern Africa. I have, however, met with undoubtedly malarial cirrhosis of the liver in Calcutta, with extensive accumulation of melanin in the greatly thickened Glisson's capsule : but this condition is much rarer in the post-mortem room there than the peculiar form of cirrhosis due to chronic kala-azar described on page 36. Much work is required before the different forms of cirrhosis of this organ in the tropics will be completely cleared up.

Although it may be impossible to decide at a single clinical examination if a given case is one of true malarial cachexia or not, yet a few days' observation will now usually allow of a correct opinion being formed. If fever is present a four-hourly temperature chart will bring out the characteristic curve of malignant tertian or other variety of malaria, as was pointed out by S. P. James, I.M.S., in a report on malaria in India. In order to obtain this typical temperature curve quinine must be first withheld for a few days, and later on given in 10-grain doses several times a day ; the fever will be controlled and completely stopped within three or four days. This will not be the case in kala-azar, in which low fever almost always follows a remission of the temperature. Finding the malarial parasite during fever will also confirm the diagnosis of that disease, although it may be complicating kala-azar, in which case quinine will fail to stop the fever, although it may lessen its height.

OTHER COMPLICATIONS OF MALARIA

It is not surprising that in such a widespread disease as malaria very numerous complications have been described. It is, however, far from easy to discriminate between those directly or indirectly due to the malarial infection and those arising from accidental concomitants. In the following list only cases in which malarial parasites have been demonstrated are included.

Nervous System.—Apart from cerebral symptoms in acute pernicious malaria, the following early and late complications of malaria affecting the nervous system have been recorded. Transient hemiplegia, symptoms resembling meningitis, especially in children, and including Kernig's sign, cerebellar symptoms—tetanus-like spasms, optic neuritis, amaurosis, retinal haemorrhages, aphasia, tremors, insanity, including mania in predisposed subjects, pseudotubes, disseminated sclerosis, herpes, neuralgia and neuritis of varying distribution, including wrist drop, musculo-cutaneous paralysis, and oculomotor paralysis, etc.

The Lungs are less affected by malaria than most important organs. Pneumonia, with a temperature curve closely resembling that of malaria, has been recorded, and I have seen one such case, while low asthenic types of pneumonia may complicate severe cases. Bronchitis (Deeks), asthma, dyspnoea with cyanosis, congestion and haemoptysis have also been reported.

The Liver in acute pernicious malaria is enlarged and congested, while jaundice occurs if much blood destruction takes place. Hepatitis has been described, but it is doubtful if suppuration ever occurs in malaria uncomplicated by amoebic disease. In chronic malaria the liver may also be enlarged, and much discussion has taken place regarding the production of cirrhosis of this organ by chronic malaria. Pathologically deposit of pigment with slight increase of the fibrous tissue in Glisson's capsule undoubtedly occurs, and I have seen such cases, but I have never seen malaria produce ascites or other clinical symptoms of cirrhosis of the liver, although that complication is a common one in kala-azar, as I have shown, and was formerly often mistaken for a result of malaria. Nicholls has described a form of cirrhosis in malaria due to perihepatitis affecting especially the portal fissure producing a monolobular biliary cirrhosis.

The Kidney suffers severely in the blackwater fever complication of malaria, as described under that heading. In addition, Deeks, in an analysis of over 50,000 cases of malarial fever in the Panama Canal Zone, found nephritis to be a common complication which disappeared in the great majority of cases during convalescence, but sometimes persisted and ended fatally with necrosed foci in the organ, as well as in the liver and spleen. H. Brown found experimentally that alkaline haematin injected intravenously in rabbits produced degenerative changes in the kidney. Asthenia and low blood pressure due to malarial infection of the **suprarenals** has also been described.

The Cutaneous System may frequently show urticaria and even dermatitis (Deeks), while purpuric haemorrhages have frequently been recorded. Haemorrhages from the nose and gums also occur.

The Spleen, apart from the simple enlargement, has several times been recorded as undergoing spontaneous rupture with fatal haemorrhage, three instances having been met with among 30,000 cases of malaria by Davidson at Panama, including one case of recovery after removal of the organ, while Noland and Watson record three such cases operated on with two recoveries.

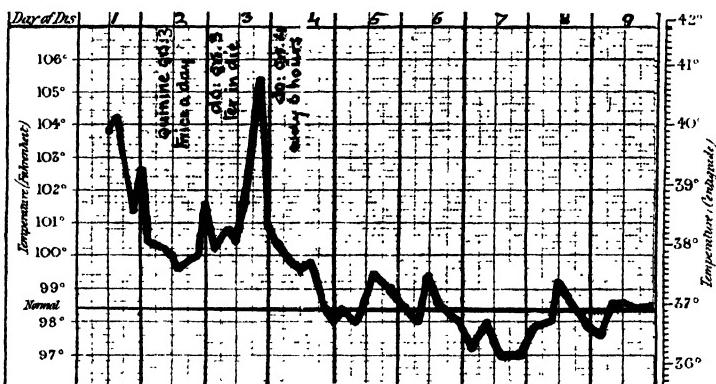
Among rarer complications may be mentioned symptoms simulating appendicitis, which has led to a needless operation, gangrene of a limb necessitating amputation; rheumatic symptoms with lumbar pain or multiple arthritis and even pericarditis, yielding to quinine treatment (Barlow); orchitis and maninitis and a large haemorrhagic cyst of the gall-bladder with crescents in the evacuated blood (de D. Figueiredo).

THE TREATMENT OF MALARIAL FEVERS

The curative treatment of malaria may be summed up in one word—quinine. There is no other drug to be compared with it for a moment, while in the rare cases in which it cannot be successfully given by the mouth it can be got into the system in other ways. There is no drug which has a truer specific action than quinine, for it destroys the actual cause of the disease. The dosage and methods and duration of administration, therefore, are of great practical importance.

I have already given data to show that 10-grain doses three times a day are sufficient to cut short an ordinary attack of malarial fever in one to four days, while four to six such doses in the course of the twenty-four hours do not have any more rapid effect, although they are advisable if the infection is found by the microscope to be a severe one. In children there is a tendency to give too small doses of this drug. One grain for each year

CHART 54 (Case 36)



Malignant tertian malaria in a child of 6, not checked by 6 to 9 grains of quinine daily, but yielding to 16 grains in the twenty-four hours.

of age may safely be given two or three times a day up to the age of 10, so that over 10 years a full adult dose should be given twice a day. Infants may receive

2- or 3-grain doses twice a day. It is often well to guard against the depressing effects of the drug by the addition of an appropriate dose of liquor strychninae, especially when large doses are being given several times a day. Chart 54 illustrates the necessity of considerable doses of quinine in the malaria of children. The patient was a European girl aged 5 years admitted for a severe malignant tertian infection with numerous parasites in the blood. Three grains of quinine were given twice a day, and raised to three times on the following day. Nevertheless, the temperature remained of the remittent type and rose again on the third evening after admission to 105·4° F., a very high point for a malignant tertian. On increasing the quinine by 4 grains every six hours, that is, up to 16 grains in the twenty-four hours, the fever rapidly yielded.

Hour of Administration.—It has been shown in the introductory chapter that all the older writers insisted that quinine should be given only during an intermission or at least a remission of a malarial fever. In fact, during the forty years that Johnson's teaching held the field it was strictly forbidden to give any cinchona or quinine until the fever had entirely ceased, and, according to some, not until the tongue had cleaned. Edward Hare who, single-handed, broke down this system and reintroduced the practice of the ship's surgeons of the later part of the eighteenth century, of giving cinchona during the fever, reduced the death-rate from fevers twelve-fold in one year at the European Hospital, Calcutta, and since his day quinine has been given fearlessly during actual pyrexia and utterly irrespective of the period of the paroxysm in which the patient comes under observation. Nevertheless, the prejudice of the dark age of British medicine in India against giving quinine during fever is still frequently met with, chiefly, although not entirely, among Indian practitioners. Theoretically the best time is during sporulation of the parasites, when the youngest forms will be free in the blood stream, while clinically there is some ground for giving the drug during a remission or intermission, as it is less likely to produce sickness or distress at that time. Practically, quinine is efficient when administered at regular intervals, irrespective of the temperature curve, while to wait for an intermission or well-marked remission may cause a fatal delay in the most severe cases, such as that of Chart 53. As a general rule, then, quinine should be given without regard to the temperature and without waiting for an intermission of the fever, but it may sometimes be advisable to throw in a larger dose, such as 15 or 20 grains, during a remission or intermission of the pyrexia.

Quinine Orally. The Duration of Quinine Administration necessary to eradicate the Infection.—It is simple enough to stop the febrile paroxysms of malaria for a time in most cases, but it is much more difficult, and also much more important, to eradicate completely the infection from the system and so prevent recurrences of fever apart from new infections. This requires much more prolonged quinization, and the essential point to remember is that a full treatment of malaria from the commencement of the first attack in sufficient doses will quickly result in the complete cure of the patient, although if thorough and early treatment is not adopted and resistant forms are allowed to develop, it will then be a much more difficult matter to rid the patient of the infection, and may prove impossible to do so in some cases without very prolonged treatment. It is generally recognized that about seven days are necessary for gamete formation, so that efficient treatment is especially

necessary during this period after the primary infection shows itself in fever. Much work has been done during the second decade of the present century on this subject, and the following conclusions have been arrived at by competent workers. Deeks, as a result of an analysis of over 50,000 cases treated in the Panama Canal Zone, advises 15-grain doses of quinine three times a day until the temperature has been normal for four days, followed by 10 grains three times a day for a week and 20 grains daily for another week. To open the bowels on admission 3 grains of calomel followed in eight to ten hours by half an ounce of mag. sulph. was always given in addition. McGilchrist also advises large doses every eight hours to keep up an even concentration of the drug in the blood. W. M. James of Panama advises quinine in solution, beginning with a dose of 20 grains of the sulphate and a purge, followed by 15 grains three times a day for a week or for five or six days after the temperature is normal and 30 grains daily for ten days more. This treatment has been much more successful in preventing relapses in his experienced hands than the former treatment with 10 grains thrice daily. If the infection is very severe he increases the quantity to 15 grains four times a day. D. Thompson also urges the early and thorough quinine treatment, giving 30 grains daily in solution for at least three weeks, this being the minimum curative quantity as shown by his observations of the blood. In only 1 out of 200 cases did the parasites resist this dosage. Very similar dosage has been adopted in the British Army after much experience, 20 to 30 grains daily being found sufficient to subdue the fever and reduce the non-sexual parasites, after which quinine, combined with arsenic and iron, should be continued for some time. Bentley in India advises 20 grains a day for three weeks in $3\frac{1}{3}$ -grain tablets as long as they are readily friable. Such complete treatments are now sold in small bottles at about cost price by the Government in India and are largely used in Bengal. In this way the people are being taught to take adequate curative doses instead of the former piece packets, which stopped the fever for a time only and led to its being discredited through the frequency of relapses owing to a cure not being effected.

Small Doses of Quinine frequently repeated have been advocated by several workers as being more efficient than larger ones less frequently. Thus Boyd, after an initial dose of 10 grains, advises 3 grains every three hours or 4 grains every four hours until the fever has ceased for two or three days. Half this amount should then be given daily for several days, followed by 10 grains every other day for two or three months, with a 15-grain dose once a week, to prevent relapses. Job and Hertzmann in Morocco gave 0.25 gm. (4 grains six times a day for a week), gradually reducing the doses by one daily until four doses are given on three days only of the fourth week. Oschsner goes even further and gives 2 grains every two hours, day and night, for sixty hours, omits the drug altogether for five and a half days and then repeats the same course, and he claims good results and few relapses.

The foregoing experience may be briefly summed up as indicating 10- to 15-grain doses of quinine being given in solution three times a day, preferably at eight-hour intervals, while if preferred and feasible, the same total quantity may be given in more frequent smaller doses. In severe cases, and when pernicious malaria is prevalent, it is better to increase the dosage to 15 grains four times a day. The full doses should be continued until the

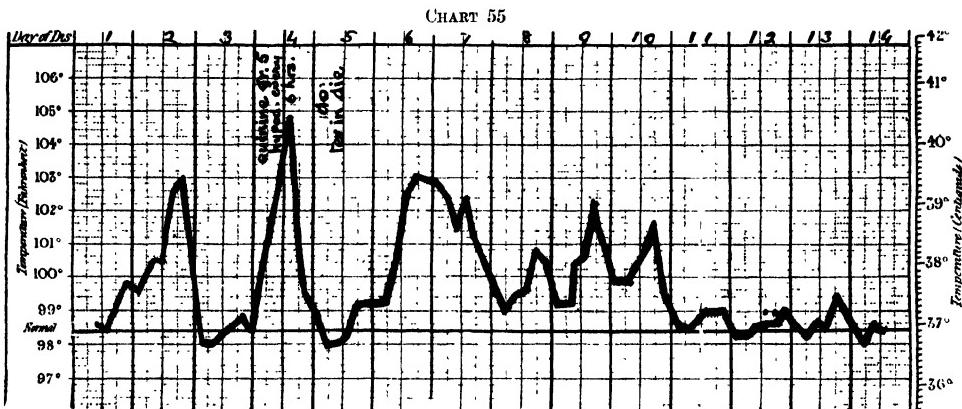
temperature has been normal for at least five or six days, after which 20 or 30 grains a day should be given for two weeks, making at least three weeks in all on such doses. If the case is treated early in a primary infection, this course will usually suffice to cure the patient, but if the case is a relapsing one, prophylactic doses, as advised under that heading, should be continued for at least another two months, not less than 10 grains every other day being taken. Even in primary infections such preventative doses may with advantage be continued for a month after the completion of the curative course, and should in every case be continued during the malarial season as long as the patient resides in a highly malarious place.

Sir Ronald Ross has recently recorded the experience of a number of Army medical officers regarding the treatment by various methods of 2460 cases of malaria, mainly benign tertians from the Salonica front. The fewest relapses occurred under the following treatment by M. Harrison. During twelve days in bed 15 grains of the bi-hydrochloride of quinine were injected intramuscularly daily in each deltoid muscle, and 10 grains of the hydrochloride were given three times a day in a mixture, making a total of 60 grains daily. Each dose of the quinine mixture also contained Liq. arsenic. hydrochloride m. 5, Tr. ferri perchloridi m. 5, Liq. strychn. m. 5, Acid. nitrohydrochlor. dil. m. 5, and Magnes. sulph. grs. 30, and was given after food. At the end of twelve days the mixture was given four times a day with the addition of quin. hydrochlorid. grs. 5 and Acid. nitrohydrochlor. dil. m. 5, making 60 grains of quinine daily for three days, after which the patients received grs. 5 of quinine hydrochloride four times a day for fourteen days.

Hypodermic, Intramuscular and Intravenous Injections of Quinine Salts.—In the great majority of cases of malaria, especially in areas in which pernicious cases are rarely seen, oral administration of quinine gives satisfactory results. Nevertheless, in the more virulent types of malaria, with very numerous parasites in the peripheral blood, often complicated with persistent vomiting, patients may sometimes be lost through relying solely on quinine by the mouth even in full doses, while in those presenting pernicious and especially cerebral symptoms it is unsafe to rely on oral administration. Moreover, although in the vast majority of the ordinary less virulent types of malaria the fever readily yields within two to seven days to quinine by the mouth, cases have frequently been reported in which the temperature was more amenable to injections of the drug. Once more, vomiting may be so persistent during malarial attacks as to create difficulties in getting sufficient quinine by the mouth retained and absorbed to control rapidly the fever, in which case injections of the drug are both much more effective and far less distressing to the patient. With increasing experience some of the disadvantages of the injection methods have been overcome and they are being increasingly used with advantage in malaria. The different methods of administering them, therefore, require careful consideration.

The Hypodermic Method.—Up to comparatively recently this has been the most commonly employed method, although it presents several disadvantages which led Ronald Ross, the writer and others to disapprove of it. In the first place it has been shown by experiments on animals that the quinine salts are largely precipitated in the subcutaneous tissues, so that much of the drug can be recovered from them even twenty-four hours after

administration. In consequence of this, as Ross has pointed out, a patient may die for want of quinine in his circulation, while efficient doses of the drug lie unabsorbed in his tissues, and the action of the drug thus given may actually be slower than when used orally. Chart 55 is that of a malignant tertian malaria in which the fever lasted for seven days,



Severe malignant tertian malaria running a prolonged course under hypodermic injections of quinine.

in which 5-grain doses of quinine bi-hydrochloride were injected four times on the first day and three times a day later, the temperature being more prolonged than with oral administration of the drug. Larger doses should, however, have been injected to get a quicker result. J. W. D. Megaw, I.M.S., also used 10-grain doses hypodermically in Calcutta, but found the temperature took on the average twelve hours longer to fall to normal than when the same amount was given by the mouth.

Another serious drawback to the hypodermic method is the frequency with which fatal tetanus has followed its use, several such cases having been reported in India. Semple, as a result of certain experiments on animals, suggested that such a disaster might possibly occur, in spite of efficient precautions as regards sterility of the solution and syringe, as a result of tetanus spores lying latent in the human body finding their way to the site of injection and developing there, but his experiments have been severely criticized on the ground of the relatively enormous doses he injected into guinea-pigs, namely, the equivalent of over 100 grains in a man of eleven stones, so they may be discounted. Nearly all authorities are now agreed that, provided proper sterility is ensured, the danger of tetanus may be ignored. On the other hand it must be remembered that the precipitation of quinine in the tissues forms a suitable nidus for the development of tetanus if its spores are injected through deficient technique, which accounts for the far greater frequency of tetanus after quinine than after injections of freely soluble salts such as morphine, etc. Quinine solutions for injection should therefore be sterilized under pressure in an autoclave, and not simply boiled for a minute or two. As hospitals possess autoclaves for sterilizing dressings, this is usually quite feasible, while in their absence ampoules of reliable firms should be used.

The occurrence of induration or abscesses after quinine injections is also due to faults in technique and to the use of a relatively insoluble salt of quinine. The bi-hydrochloride is the salt of choice for both hypodermic and intramuscular injection, while I have recently found that the still more soluble cinchonine bi-hydrochloride is also very efficient, being more rapidly absorbed and causing less local pain and irritation in my experience than the corresponding quinine salt. I have also used both quinine and cinchonine acid hydrobromide with success by each of the injection methods.

The following opinions of workers on malaria will suffice to indicate the present position of the hypodermic method of administering quinine. Its use is supported by W. M. James, who gives $22\frac{1}{2}$ grains ($1\frac{1}{2}$ grammes) of the bi-hydrochloride dissolved in 20 c.c. of normal salt solution deep into the subcutaneous tissues when vomiting is present. Webb, who experimented with the method in monkeys and concluded—contrary to the opinion of McGilchrist based on experiments on guinea-pigs—that quinine sulphate in dilutions of from 1 in 8 to 1 in 2 both hypodermically and intramuscularly were readily absorbed and were more efficient than similar doses by the mouth, and Abrami, working in Macedonia, injected hypodermically at least 2 gm. of quinine daily in cases with crescents and in those which had become chronic. On the other hand, Ronald Ross, Soulié and Laveran are opposed to the hypodermic method, the last two having seen necrosis and ulceration follow it: possibly due to the injection being made too superficially.

The Intramuscular Method.—Provided the all-essential sterility is maintained, the objections to this method appear to be less than those of the hypodermic plan, as absorption is more rapid and induration and necrosis less frequent, and many experienced workers favour its use. Ronald Ross, however, is opposed to it for the reasons already given, as is McGilchrist, who has recorded finding precipitation of the salt and necrosis of the tissues of the gluteal muscle in a patient who died the day after an injection, but this may have been predisposed by his low condition. Sicard, Rimbaud and Roger have recorded 15 cases of sciatica with much pain and almost complete paralysis of the lower limb as a result of quinine injections in the buttock, and they recommend the injections to be given above a line drawn from the upper end of the gluteal fold perpendicularly to the axis of the body.

On the other hand, many experienced workers, especially those having to deal with severe forms of malaria in Africa, the Malay States, etc., are strongly in favour of its intramuscular use. Among its supporters may be mentioned the following: Justi, who records 2000 intragluteal injections of urea quinine with only two abscesses due to faulty technique; Clarence, with forty-five years' experience in Mauritius, who frequently found intramuscular injections succeed after oral administration had failed; Solis Cohen of Philadelphia, who also used quinine and urea hydrochloride (quinine carbonid bi-hydrochloride); Clarke in the Malay States, who found the coolies preferred it to oral administration; Neligan in Persia; Soulié in Algeria, who gave 1-gm. doses of the bi-hydrochloride with 0.5 gm. urethane in 3 gm. distilled water intragluteally twice daily for three days in the week for four to six weeks, with rapid reduction of the fever and of the spleen. All the above workers found intramuscular injections more powerful than oral administration, and some

of them recommend it as the routine method of treatment of malaria. Stephens and his colleagues found one or two injections of 15 to 30 grains of an insoluble form of quinine intramuscularly stopped the fever and caused the benign tertian malaria parasites to disappear, but the majority relapsed within two to four weeks.

The above evidence is clearly in favour of sterile intramuscular injections of quinine in cases of malaria which resist oral administration, and under certain conditions, such as when severe and resistant cases of malaria predominate and under military conditions demanding rapid and complete cure, this method may sometimes be used with advantage as a routine measure.

The Intravenous Method.—It appears to be obvious that the most rapid and efficient way of obtaining the specific action of quinine on the plasmodium malaria is to inject a soluble salt directly into the circulation. That this is both feasible and effective has been abundantly proved by the successful treatment by this method of intense infections, frequently with cerebral symptoms, in which too often other methods of administering the drug do not act sufficiently quickly to save the patient. The method, however, is not without danger, sudden deaths having occasionally rapidly followed such injections, and, although introduced by Bacilli many years ago in Italy, it is only within the last two decades that technique required for its safe use has been worked out, and has led to the more general adoption of the intravenous method, some workers now even advising its routine use in all malaria infections. Two cases in which dangerously numerous malignant parasites were found on microscopical examination of the blood, one of whom showed pernicious symptoms and the other did not, but who were both successfully treated by intravenous injections of quinine, have already been given (see page 244). They illustrate the class of cases in which this method of treatment is imperative in order to save the life of the patient. Authorities differ regarding the frequency with which this potent method should be employed, but the following indications may be laid down for intravenous injections of soluble quinine salts :

1. In all severe malarial fevers showing the slightest indication of pernicious symptoms, including the cerebral and intestinal forms of malaria, in which it should never be omitted.
2. Severe cases of malaria with high fever and much sickness, making it difficult to obtain rapid absorption of the drug when orally administered.
3. Very numerous malignant tertian parasites, such as half-a-dozen or more in every field of an oil immersion lens, especially if of the malignant tertian variety, as in the cases given on pages 244 and 261.
4. In view of the number of observers who have recorded very favourable results of the routine intravenous use of quinine, it is also justifiable to adopt this method, with the precautions noted below, when severe malaria with pernicious cases is very prevalent and the circumstances do not permit of microscopical examinations of the blood to ascertain the degree of infection in each case, as under such circumstances some lives may be lost by trusting solely to oral administration.

The Quinine Salt most generally used for intravenous injection is the bi-hydrochloride on account of its great solubility, namely, 1 in 1. I have recently investigated the suitability of the more soluble quinine salts for intravenous injections, and found

the acid hydrobromide to be the least toxic, while as its solubility is 1 in 7 it can easily be given in sufficient doses in a 10-c.c. syringe. R. Knowles has also reported favourably on its intravenous use in malaria in Assam. Quinine urea, with a solubility of 1 in 1, is also suitable and convenient for this purpose. Some workers have used the bi-hydrochloride in combination with urethane intravenously in pernicious malaria with good results, Soulié recommending 1 gm. of the quinine salt with 0.5 gm. of urethane for this purpose, while Carnot and De Kerdrel gave 0.4 gm. of the quinine with 0.2 gm. of urethane in 20 c.c. saline solution. I have also found that cinchonine bi-hydrochloride and cinchonine acid hydrobromide, in similar doses to the corresponding quinine salts, are very suitable for intravenous as well as for intramuscular injection, while they are more soluble than the quinine salts.

The Dosage of quinine salts recommended for intravenous use is generally 10 to 15 grains, but caution is necessary in this connexion to avoid any risk of fatalities occurring which would be liable to bring a life-saving method into disrepute. Personally I think it is advisable for any medical man, before giving quinine salts intravenously in malarial patients, to do a few experiments on rabbits, injecting subminimal lethal doses as well as fatal ones, as this will impress on him the narrow line separating them. The death in a few seconds with convulsions produced by a dose only just sufficient to prove fatal, evidently through direct action on the central nervous system (as no thrombosis may be found after death), will ensure his taking the necessary precaution of injecting his doses very slowly. I never give more than 10 grains for the first intravenous dose, except in very urgent pernicious cases, and if the patient is in a feeble state prefer to give only 7½ grains or 0.5 gm., increasing the dose gradually to 10 up to 15 grains if well borne. Bass advises that the intravenous dose should never exceed 10 grains. I do not think that 15 grains should ever be exceeded, especially as it seems to be sufficient for all purposes, and it is much safer and at least equally effective to use smaller doses and repeat them when necessary.

The Dilution of the Solutions of Quinine Salts used for Intravenous Injection has given rise to much difference of opinion. McGilchrist writing in 1913 took the extreme view that 7 grains or so of the bi-hydrochloride should be dissolved in two or three pints of normal saline for this purpose, which would make the method quite unpracticable in the vast majority of cases. Deeks used a dilution of from 1 in 250 to 300; Barlow dissolves his dose in 600 c.c.; Soulié advises a large amount of solvent, and Barbary dissolved 1 gm. in 125 c.c. of saline. T. E. Wright, who first gave a dose in 240 to 300 c.c., subsequently reduced the quantity of fluid to 20 c.c.; Shircore gave 10.34 grains in 1 c.c. Bass, Cornet and De Kerdrel, Richet and Griffin, McClean, Rogers, Knowles, J. D. Thomson and Stephens have all used concentrated solutions of quinine salts with favourable results. In 1917 I carried out a series of experiments on rabbits and pigeons to test this point, and found the minimal lethal dose of the bi-hydrochloride of quinine intravenously was the same whether the dilution of the solution injected was 1 in 10, 1 in 20, or 1 in 100, and only very slightly higher in 1 in 5 solution, while other salts gave similar results. Moreover, in a case recorded by Brodribb rapid death occurred from the action of the drug although the dose was given in a pint of saline, showing that a high degree of dilution did not avert

the toxic effect, while such large amounts of fluid may well prove too much for a weak heart, as has been pointed out by others.

The Rate of Injection appears to me to be the crucial point here, as by dissolving the dose in about 10 c.c. of saline, allowing of easy injection with a hypodermic syringe, and by taking some time over the actual injection the drug is diluted in the blood to a safe point before it reaches the brain and heart as I have pointed out elsewhere. J. D. Thomson also lays stress on this point and advises the use of a 20 per cent solution, using 15 grains of the bi-hydrochloride in 5 c.c. saline and taking 15 to 20 seconds over the injection of each c.c., which appears to be a safe rule. This question of greatly diluted *versus* concentrated solutions is of practical importance, as the injection of a dose of quinine with a 10-c.c. syringe is a far simpler and quicker procedure than running several hundred c.c. of fluid into a vein, and the establishment of the simpler procedure as a safe one renders this invaluable method of treating malaria much more readily available in practice.

Arsenic in Malaria.—After quinine, but a long way after, comes arsenic in importance in the treatment of malaria. In chronic infections the drug appears to be of some use against the parasite, especially when combined with small doses of quinine, but it is also of benefit in stimulating the reproduction of red corpuscles, and so combating the anaemia resulting from destruction of the red corpuscles by the parasites, for which purpose it may be given in the form of liquor arsenicalis in 5-minim doses three times a day. The introduction of organic compounds of arsenic in the treatment of syphilis naturally led to their trial in malaria as well, and a definite destructive action of **salvarsan** of limited degree on the parasites was found by Werner and by Summa, especially against the benign tertian form, although many cases relapsed. Stott found slight action on the asexual stages of the parasites only. **Neosalvarsan** has also been used with very similar results, although Linnell in the Malay States considered it the best remedy for relapsing forms of malaria, but Silatschek and Falta used it in over 100 cases, and concluded that it was of very little use in chronic malaria and inferior to intravenous injections of quinine, and Stein in Albania found it only acted to any extent on benign tertian parasites, and not on the more important malignant tertian variety. **Dimethyl-arsenate of soda (arrhenal)**, in 5- to 10-centigram doses hypodermically in combination with 0.5 gm. of hydrochlorate of quinine, has been recommended by Gautier as a cure for the most obstinate cases of malaria, and Ravaut and others also commend 20 to 30 centigrams of arrhenal subcutaneously, together with 2 gm. of quinine by the mouth, in chronic malaria. **Soamin** in 1-grain doses intramuscularly combined with quinine by the mouth is reported on favourably in malignant tertian malaria by Dunley-Owen. **Hectine** has also been used, and is of some value in combination with quinine in doses of 0.1 to 0.2 gm. (1 to 3 grains) intramuscularly, especially in chronic cases, although not of much value in itself.

Among other drugs which have been recommended in the treatment of malaria are **methylene-blue** in 2- to 4-grain doses in pill form, which, although much inferior to quinine, may be of some service in the rare cases of idiosyncrasy to quinine. One-grain doses may also be given hypodermically, while Appel has recommended 10-c.c. doses of a filtered and carefully sterilized 2 per cent solution of methylene-blue intravenously in malaria, which turns the skin bluish-green for a few minutes. He used salvarsan separately in

the same cases so it is difficult to appraise his results. Barlow has tried intravenous injections of perchloride of mercury in doses of a grain in 10 c.c. normal saline intravenously, and states that when used in addition to quinine the spleen is more rapidly reduced than by quinine alone, and that the chemical has some action of itself on the malarial parasites, but Lyons failed to confirm this. Enzymes hypodermically have also been recommended, but this claim also lacks confirmation, and a careful investigation by Stephens showed it to have no action against the malarial parasites. Radium and X-rays have both been reported as beneficial in chronic malarial splenomegaly, but the reports are not unanimous on the subject. The writer observed the disappearance of crescents in three cases following the intravenous injections of tartar emetic, and suggested further trials. Watkins-Pitchford and Orenstein in South Africa obtained similar results in twenty-four consecutive cases after quinine had failed, but a number of other workers have reported negative results, so this method does not appear to be likely to prove of much value.

BLACKWATER FEVER

Blackwater Fever is the most serious complication of malaria, and is characterized by the appearance of haemoglobin in the urine due to the rapid dissolution of the red corpuscles of the blood, although the precise manner in which this is brought about is still obscure. It must be borne in mind that a similar pathological condition may occur apart from malaria, such as in paroxysmal haemoglobinuria, which may lead to confusion. The dependence of true blackwater fever on previous malaria is disputed by some, but most of the best authorities, who have had much actual experience of the disease in the endemic areas, agree on its malarial origin, as will be shown later.

Geographical Distribution.—The distribution of blackwater fever may be somewhat less wide than that of malaria itself, because it is only commonly met with in the more intensely malarious areas with high endemic indices, and in which the malignant tertian form is the predominating one, this complication being most closely associated with that variety, although occasionally occurring in benign tertian or still more rarely quartan forms.

Africa, many parts of which are intensely malarious, and in which the great majority of infections are of the malignant or subtertian variety, is the great home of blackwater fever. The West Coast colonies, including North and South Nigeria, Sierra Leone, the Gold Coast, French, Belgian and Portuguese West Africa, etc., all suffer severely. It is also widely prevalent in East Africa, Nyassaland, and has been reported from Abyssinia, Rhodesia, where it is diminishing with opening out of the country, and in Algeria, especially near the coast (Parrot).

Asia is less subject to the disease while the endemic areas are smaller and more localized than those of Africa. Thus it has been recorded in Palestine (David and Yofe), Formosa (Hatori), Tonkin and Cochin-China, while two cases have been reported recently (1916) from China, although Maxwell previously considered that the disease had not been proved to occur there, so it must be rare. The Dutch East Indies also report the disease.

In **India** the relationship of blackwater fever to places with high endemic indices for malaria is well brought out. Thus Stephens and Christophers found the disease in the Duars at the foot of the Darjeeling Himalayas and at Jeppore State in Madras, in both of which the endemic index reached the extreme figure of 80 to 100 per cent, while it has been recorded in Assam by Powell and others, in parts of which the endemic index reaches over 80 per cent. Very malarious parts of Upper Burma also show cases, as do the contiguous highly malarious Malay States as shown by Fraser. I have also seen cases from the southern malarious parts of Chota Nagpur. On the other hand, the disease very rarely occurs in the neighbourhood of Calcutta (except as imported cases) and most other parts of the Indian plains where the endemic index is comparatively low. In Ceylon Castellani records only imported cases.

In **America** the disease occurs in the Panama Canal Zone and other parts of Central America, as well as in Haiti and other West Indian islands. A number of cases have been reported from the malarious Amazon Valley of Brazil, and in other South American countries. The Southern United States also suffer.

In **Europe** Castellani mentions South Italy, Sicily, Sardinia, Greece and Southern Russia as affected, while cases have recently been reported from South Albania.

The Relationship of Blackwater Fever to Malaria.—The above-mentioned geographical distribution of blackwater fever clearly brings out the close association of the disease with intense foci of malaria. The occasional occurrence of haemoglobinuria in non-malarious parts is readily explainable on the ground that they are probably of the nature of paroxysmal affection due to chills, etc., in persons predisposed to dissolution of their red corpuscles, and so are of no weight in the argument. In his review of Tropical Medicine in 1911, A. Balfour stated that most of those with a practical experience of the condition were agreed that it is a manifestation of malaria, and a little later he was inclined to the belief that blackwater fever is more a "symptom complex" than a well-defined disease, probably due to depressing influences acting in conjunction with the malarial toxin. Among strong supporters of the malarial origin of the disease are Stephens and Christophers with African and Indian experience; Deeks and W. M. James of Panama; A. Plehn, West Africa; Barratt and Yorke of the Liverpool School; Christophers and Bentley, with experience in the Duars in India; Hearsay of East Africa; Deaderick of the Philippines; Lovelace of Brazil; Parrot of Algeria; Fraser of the Malay States, and others, all with practical experience in the endemic areas.

On the other hand, we have the authority of C. F. Craig and others, who believe blackwater fever to be a specific disease due to an undiscovered organism, supported by Leishman, who has described cell inclusions in large mononuclear leucocytes in slides sent to him in London from Africa, but which Low and Wenyon consider certainly not to be parasitic in nature. Coles has also described what he thought to be protozoal parasites, but his observations have not been confirmed.

This question is far from being of purely academic interest, as both the prophylaxis, and to some extent the treatment, depend on the view taken regarding it. The **length of residence in an endemic area before blackwater fever usually appears** seems to me to be

of crucial importance in this question. Many of the most experienced workers concur that this serious and alarming complication very rarely if ever appears until the patient has lived from several months to a year or more in a highly malarious area, and has suffered from repeated attacks of malaria, for which, as a rule, quinine has only been taken intermittently, and not sufficiently regularly or fully to eradicate the malarial infection. In the case of susceptible persons going to reside in the endemic area of a specific disease for the first time it is during the early period of their stay that they are most liable to contract such a disease, and to a less extent after they have been living for a year or more in the place. This is a strong argument against the disease being a special specific one, while it is in complete accordance with blackwater fever being due to some alteration in the blood brought about by repeated attacks of malaria predisposing to extensive dissolution of the red corpuscles when some exciting cause, such as a chill or a sudden large dose of quinine, occurs.

The results of the inquiry of Christophers and Bentley into the prevalence of blackwater fever in the extremely malarious Duars at the foot of the Darjeeling Himalayas well illustrate many of these points.

The Distribution and Relationship to Malaria is first dealt with, and it is shown that blackwater fever is prevalent in precisely those parts of India which are most highly malarious, which the greater part of the country is not. The Duars is the site of the greatest prevalence of blackwater fever in India, and it presents an endemic index of approximately 100, equal to that of the most malarious parts of Africa where blackwater fever is common. Owing to the yearly arrival of susceptible people to work on the tea-gardens, the important factor of labour aggregation tends to heighten the malarial incidence in this already very unhealthy terai area. Moreover, the blackwater fever cases almost all occurred in the gardens situated in the worst part close to the foot of the hills. Europeans living here constantly suffer from attacks of fever, to which they get so accustomed that they tend to make light of them and neglect adequate treatment, as well as prophylaxis. At least fifty out of sixty Europeans resident in one area were personally known to the investigators to have had attacks of fever within a single year. Both Europeans and native babus often suffered from malarial fever every ten days or so for months at a time, and the surrounding conditions are so malarious that it would be almost impossible for them to have escaped infection, neglecting as they did all prophylactic measures.

The racial incidence showed the greatest amount of infection among Europeans, and next in the native babu class from less malarious parts. Chinese carpenters also suffered, while three attacks were seen in Indian coolies.

The seasonal incidence showed the greatest prevalence in the more malarious last two quarters of the year, as seen from the following figures :

First quarter.	Second quarter.	Third quarter.	Fourth quarter.	Total.
8	16	31	25	83
Under 6 months.	6-12 months	12-24 months.	24-36 months.	36-48 months.
0	8	40	12	5
				1

The effect of **length of residence** in the Duars is shown from the following data :

The absence of the disease in the first six months of residence in the endemic area is very remarkable if the disease be a specific one. The great frequency of attacks in the second and third years of residence in a very malarious area is most striking. Second attacks most frequently occur during the first year after the primary one, and especially during the first six months. Third attacks are much less frequent in the Duars than second ones. After five years' residence there is much less liability to attacks. Infection occurs earlier and more severely in those who have been especially subject to malaria. Thus, the more minutely the conditions are examined the more intimately is blackwater fever found to be associated with malaria.

The parasite most commonly met with in blackwater fever is the malignant tertian, the other forms being rare. The most minute scrutiny of blood slides from cases of the disease failed to reveal any other parasites than those of malaria. Moreover, a greater incidence of malaria was found among blackwater fever cases than in the rest of the community, but the parasites disappear from the blood during an attack owing to the dissolution of the damaged corpuscles containing them.

All these facts go to show that in the absence of any direct evidence of the occurrence of a specific organism in blackwater fever apart from the malarial parasite, taken with the intimate association of the disease with prolonged exposure to highly malarious conditions, there can be no reasonable doubt that blackwater fever is but a complication of malaria, and thus an easily preventable disease.

The Frequency of Malaria Infection in Blackwater Fever Cases is also of the greatest importance, and has been closely studied by Stephens and Christophers. The question is complicated by the fact that those red corpuscles which are damaged by being infected with malarial parasites are among the first to be dissolved, so the plasmodia tend to disappear rapidly from the peripheral blood with the onset of haemoglobinuria. Stephens has collected a series of cases in which microscopical examinations of the blood were made by reliable observers before and after the onset of the disease which showed the presence of malarial parasites in 95·6 per cent of cases examined the day before the haemoglobinuria commenced, in 61·9 per cent on the day of the attack, but in only 17 per cent on the day after. They also found in many cases other evidence of malaria such as pigmented leucocytes and a great increase of the large mononuclear leucocytes. Where complete blood examinations are available the evidence is therefore conclusive of the extremely close relationship of the blackwater fever to previous malaria, while the existence of a special parasite of the disease is purely hypothetical. We may therefore safely base our prophylaxis and treatment of blackwater fever on the assumption that it is essentially a complication of malaria of a persistent and relapsing type.

The Blood Changes.—The most interesting part of the recent work concerns the precise changes which occur in the blood in this disease, which have not previously been accurately determined. The destruction of the red corpuscles takes place in two ways. Firstly, as described by Christophers and Bentley, and confirmed by the Liverpool workers, the spleen shows extensive phagocytosis of the red cells in both large macrophages and in smaller cells, down to about the size of a lymphocyte. Secondly, an active dissolution of the red cells takes place within the circulation producing an actual haemoglobin anaemia.

Barratt and Yorke have measured the degree of this change in the plasma with the spectroscope in a number of cases of blackwater fever, in three of which the observations were made before, during and after an attack. Their method showed a small amount of dissolved haemoglobin in oxalated blood plasma of healthy men, but it rarely exceeded 15 per cent. In blackwater fever occasionally only these same small amounts were found even during an attack, but in the considerable majority the amount was greatly increased, rising to from 0·40 to 0·95 per cent. There was also a close relationship between the amount of colouring matter dissolved in the blood and the degree of haemoglobinuria present at the same time. They further carried out a series of experiments on rabbits to determine if the injection of a solution of haemoglobin into the veins would produce haemoglobinuria, and plotted out curves of the amount of this substance in the blood and the urine at different intervals after the injections. When the urine was obtained by continuous catheterization they found that the rate of excretion continues to rise for some hours after the injection until the amount in the urine exceeds that in the blood, and later it slowly falls again. It is thus clear that the presence of excess of dissolved haemoglobin in the blood does produce haemoglobinuria, and that such excess is commonly present during the course of blackwater fever.

Is Blackwater Fever produced by a Haemolysin?—In paroxysmal haemoglobinuria Doath and Landsteiner have proved the presence of a haemolysin in the blood of affected persons which may be brought into action by cooling the blood and then raising it again to body heat. They have also prepared a serum by injecting such blood into an animal, and were able to prevent attacks by its use. Barratt and Yorke failed to find such a haemolysin in blackwater fever, except to a very slight extent in one case, and they concluded that the haemoglobinuria of blackwater fever is not dependent on haemolysin anaemia. Christophers and Bentley, however, found that on injecting haemolysin into the blood of an animal it very quickly disappeared, and its presence could not be recognized by the usual tests, although it must have been present and had actually produced, in the blood and organs of the dogs used, changes very similar to those found in blackwater fever. They therefore conclude that the disease is probably due to some specific haemolysin arising in the body as a result of repeated attacks of malaria, in which frequent dissolutions of red corpuscles take place in the internal organs ; much as when repeated injections of blood are made into an animal in producing a haemolysin artificially. They also give evidence to show that anti-haemolytic bodies may be formed in the blood of a protective nature. Both the Indian and African workers mentioned agree that quinine can never be present in the system in anything approaching the quantities necessary to have a direct action in dissolving the red corpuscles. Moreover, Christophers and Bentley have not been able to confirm the observations of D. McCay to the effect that the sulphate of quinine markedly lowered the salt content of the blood and so predisposed to dissolution of the red corpuscles. They think that haemolysins are formed in malaria as a result of the constant phagocytosis of the red cells, which is most marked in the malignant tertian form, and suggest that the sudden liberation of complement in the body, in some way or other not yet understood, may possibly precipitate dissolution of the red corpuscles and an attack of blackwater fever. These important observations allow a clearer view

to be obtained of the actual occurrences in the blood in blackwater fever, and pave the way for further advances from experimental work on similar lines.

Pathology.—Although the very close association of blackwater fever with malaria is clear, the exact way in which the dissolution of the red corpuscles is brought about is not precisely known in spite of much investigation. As Christophers and Bentley suggest, during the repeated attacks of malaria which precede the onset of the affection, haemolysins may be developed in the blood as a result of frequent destruction of red corpuscles by the parasites setting free haemoglobin in the circulation. Some special condition, such as a chill or a large dose of quinine, especially when taken by a patient who has not used it regularly, may precipitate an attack, as pointed out by Koch. Many observers have noted the danger of the intermittent use of quinine in highly malarious places in predisposing to blackwater fever, as the drug thus used fails to eradicate the parasites and allows of the dangerous repeated attacks of malaria. On the other hand, Christophers and Bentley and others assert that the regular prophylactic use of quinine prevents the blackwater fever complication: a further strong point in favour of the malarial origin of the disease. Barratt and Yorke have also studied haemoglobinuria experimentally and think the condition is dependent on an accompanying haemoglobinaemia, although they are not sure where the blood is destroyed, and that quinine may act by initiating or aggravating the process in malarial subjects. It has also been suggested that the condition may be an expression of anaphylaxis to the malarial parasite. A sudden over-production of complement has also been put forward as an explanation.

Among the changes found after death are plugging of the urinary tubules by fibrin and coarsely granular casts, as described by Barratt and Yorke, to which they with justice attribute the anuria. Great destruction of the liver cells has been described by Fraser and others.

The Symptoms of blackwater fever are those of malaria with the addition of the appearance of haemoglobin in the urine in large quantities. The onset is often accompanied by a rigor.

The Urine becomes dark red or porter-coloured, and contains much haemoglobin, giving the spectroscopic bands of oxy-haemoglobin at first, but later, especially on standing, of methaemoglobin. Urobilin is present in excess, but bile pigment is not usually found. Red corpuscles are either absent or far too few to account for the amount of haemoglobin present. The reaction is acid, albumen is present in very large quantity, and Christophers and Bentley found it to be in proportion to the haemoglobin; Deaderick gave the average as from $\frac{1}{2}$ to $2\frac{1}{2}$ gm. per litre, while it may reach as high as 14 gm. Bright red crystals of haematoiodin may be found (Woldert). Granular, hyaline and tube casts made up of disintegrated blood colouring matter may be present in large amounts, especially the latter. In a fatal case the blood serum was found to contain 0.53 gm. per litre at first and 2.04 gm. later, showing retention of urea (Achard and Saint-Girons).

Suppression of Urine, due, according to Barratt and Yorke, to blocking of the tubules, especially the large collecting ducts of Bertini, with pigment derived from the dissolved

haemoglobin, which mechanically produces suppression of urine, is the most serious symptom in blackwater fever, and if it is not relieved a fatal result ensues.

The Complications are the same as those of malaria itself, cerebral symptoms being one of the most frequent.

The disease chiefly affects adults, but a number of cases in children have been reported from Africa, as has a succession of 4 cases occurring in the same house.

The Mortality and Prognosis.—The death-rate is very variable. Thus Deaderick reports 10 deaths among 34 cases, 2 from suppression of urine and 8 from exhaustion, and notes that hiccup is a fatal sign. Fraser in Malaya had 5 deaths in 18 cases ; Parrot gives a mortality of 49·1 per cent among 24 cases ; reports from British possessions in Tropical Africa for 1913 showed a mortality among 149 cases of 23·5 per cent, and varying between 10 and 35·29 per cent ; in Tonkin Boyé gives figures for twelve years showing a death-rate in Europeans of 33·2 per cent from 1902 to 1907, which fell to only 12·8 per cent during the next seven years, while in natives the figures were 22·6 and 20·9 per cent respectively.

Among **Predisposing Causes** may be mentioned first, taking a large dose of quinine for a recurrence of malaria when the drug has not been taken regularly, which may excite an attack in a patient who has suffered from repeated attacks of malaria which have not been efficiently treated with full and prolonged doses of quinine. In French West Africa Grienwank found that the onset of cold winds in the autumn at the end of September induced attacks ; while Cook observed in Uganda that relapsing fever predisposed to blackwater fever.

The Prophylaxis of blackwater fever is that of malaria. Thus the reduction in the mortality from this complication of malaria recorded by Boyé in Tonkin from 33·2 to 12·8 per cent in seven years was found by him to have been due to compulsory quinine prophylaxis among the European troops. Christophers and Bentley in their work on blackwater fever in the Duars in India obtained a very great reduction among the European tea-planters by the regular use of daily doses of 5 grains of quinine, the only three cases occurring during twelve months having occurred among those who did not believe in quinine and only took it when they felt unwell. Hatori records a great decrease or entire disappearance of the disease amongst garrison troops in Formosa as a result of anti-malarial measures. Plehn and Harford with African experience, Lovelace of Brazil, Parrot in Algeria, Yofé of Palestine all agree that regular quinine prophylaxis and other anti-malarial measures constitute the best prophylactic measures against blackwater fever, but the irregular use of quinine is stated by several to be worse than useless.

Treatment.—The most difficult problem in the treatment of blackwater fever is to decide whether quinine should be given or withheld, and the answer largely depends on whether malarial parasites are still present in the blood in any numbers. Most authorities are agreed that quinine should not be given unless the parasites are still present, and as the corpuscles containing them are likely to be rapidly dissolved, it is exceptional for them to be present except in very minute numbers only detected by prolonged microscopical

examination, and the use of quinine is then unnecessary and may be harmful. If the attack has been brought on by a sudden large dose of quinine this will be an additional reason for withholding further doses of the drug for a time. On the other hand, haemoglobinuria may result from the very severity of the attack, as in the case recorded above, with nearly half the red corpuscles infected, and in such cases quinine must be given, preferably intravenously if the infection is very great, or intramuscularly if less so, as orally administered it is likely to be rejected on account of the sickness so often present. After the attack has completely subsided quinine should be commenced cautiously, beginning with small doses such as 5 grains gradually increased, and if well borne continued sufficiently long to cure the malarial infection, which will be the most certain way to prevent a recurrence of both malarial fever and the dangerous haemoglobinuric complication. The use of quinine during the attack is advised by Fletcher of the Malay States, who noted that 2 cases with no quinine and 3 with small doses died, but 11 out of 13 treated with 15 to 20 grains a day recovered. Ott and Burkitt both advise quinine intravenously if parasites are present, while Torrance and Bowman in Haiti treated 13 cases with quinine intramuscularly with 12 recoveries. Cardamatis, working in Greece, is almost alone in advising that no quinine should be given even if parasites are present.

Next in importance is the treatment directed towards the prevention or relieving the deadly suppression of urine, with regard to which some progress has been made recently. For this purpose injections of salt solutions and the use of alkalies are the most important measures, the former to stimulate the renal secretion and dilute any toxins present in the blood, and the latter to counteract any tendency to acidosis, which has been suspected as one of the causes of the trouble. Plehn in 1908 recommended copious saline enemata in blackwater fever; Bruce-Porter gave isotonic salines intravenously with success, and Lovelace in Brazil also used normal saline to keep up the blood pressure. McCay used a hypertonic sodium chloride 1·2 per cent solution intravenously with success in Calcutta, he and W. D. Sutherland having previously proved experimentally that a high salt content in the blood greatly inhibited the action of an active haemolytic serum, and De Raadt has suggested the same measure to reduce the amount of complement in the blood, excess of which he thinks is the cause of the dissolution of the red corpuscles. Grienwank employs a 1·5 per cent sodium chloride solution with 15 per cent of serum, which he thinks makes it less irritating to the kidneys. McCay advises the use of hydrochloride of quinine rather than the sulphate, as he states it has less haemolytic value, but McGilchrist disagrees with this view, as do Christophers and Bentley.

Alkalies form an important part of Hearsay's treatment of blackwater fever, which has been largely adopted in Africa. He gives 10 grains of sodium bicarbonate with 30 minimis of Liquor hydrargyri perchloridi every two hours for the first twenty-four hours and then every three hours until the urine is free from haemoglobin, and records eighteen successive recoveries. Isher, however, cautions against Hearsay's treatment in the absence of medical help, as he has seen mercurial poisoning follow it. Torrance and Bowman gave 30 grains of sodium bicarbonate in a pint of water both by the mouth and rectum and with good results, while T. E. Wright used the same salt orally, subcutaneously and together with glucose intravenously. Calcium chloride in 4- to 6-gramme doses by the mouth or

1 to 2 grammes subcutaneously was advised as long ago as 1905 by Vincent for its anti-haemolytic action, and has been also used by Bellet and by Burkitt with success. Sorel has reported six successive recoveries after the use of isotonic lactose and glucose solutions made up of 9·25 per cent of lactose or 4·7 per cent of glucose. He advises 250 c.c. subcutaneously on three consecutive days in the morning and 700 to 800 c.c. by the rectum in the evening. In a grave case 250 c.c. intravenously was most beneficial. Alcohol and cold sponging are to be avoided in blackwater fever. Incision of the capsule of the kidney was tried in one case by Stannus for suppression of urine without success.

The success of the above methods of treatment strongly indicates that a diminution of the alkalinity of the blood plays an important part in producing the suppression of urine in blackwater fever, just as I have shown it to do in that of cholera, so large amounts of bicarbonate intravenously are worthy of trial, as by this means I have during the last three years reduced the death-rate from suppression of urine by, in cholera, 70 per cent.

Among other remedies salvarsan and neosalvarsan have been tried without much benefit. Morphia has been advised by Plehn for extreme restlessness, but is better avoided if the renal functions are deficient. A blister over the left pneumogastric nerve has been suggested for persistent vomiting.

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XIII. EPIDEMIC DENGUE—SPORADIC DENGUE OR SEVEN-DAY FEVER—PAPPATACI OR THREE-DAY FEVER

Introduction.—In the literature of dengue up to the end of the nineteenth century the disease is described as occurring in epidemics at variable but usually long intervals, spreading over wide areas and a number of countries and attacking the great majority of the population. During the last two decades the increasing use of microscopical methods of diagnosis in fevers in the tropics has led to clearer ideas regarding the limitations of malarial fevers, with the result that other fevers of short duration, previously erroneously regarded as malarial, have been recognized. The most important are that described by the writer in 1905 as "A common sporadic seven-day fever of Indian ports simulating dengue," and "Three-days' fever of Chitral" described in 1906 by McCarrison and a very similar fever to the last described by R. Doerr in the Balkan Peninsula in 1908, now known as Pappataci or three-day fever. After studying the older literature of dengue, especially in India, the writer came to the conclusion that his Calcutta seven-day fever differed so much in its longer and sometimes continued temperature curve and its yearly sporadic incidence from the classical epidemics of dengue as to be a distinct fever, and McCarrison came to a similar conclusion regarding the Chitral three-day fever.

In 1907 Ashburn and Craig recorded a careful clinical and experimental investigation of an outbreak of dengue in the Philippine Islands which closely resembled the Calcutta seven-day fever, and in the following year H. Fooks recorded three-day and seven-day types of dengue in the Punjab. In 1909 J. W. D. Megaw discussed the whole question in the light of accumulating knowledge, and adduced strong arguments in favour of his view that there was not sufficient evidence to allow of the newly described fevers being differentiated from dengue, of which they should be considered to be varieties. Although this conclusion was at the time disputed by Rogers and McCarrison, it has since met with increased and very general acceptance. More recently Harnett has shown that the blood changes in both the seven-day and three-day types of fever are identical, including the increase in the eosinophiles during convalescence. It will not be possible to settle this vexed question until the causative organisms of these fevers are discovered, and it is proved or disproved that they belong to a group of parasites, such as those of malaria, with different varieties producing slightly varying types of fever. A great advance has been made by the differentiation of this group of fevers from malaria, with which they were formerly nearly always confused in India. However, in our present state of knowledge it will be best to describe them together with dengue, although there is probably a better

case for differentiating "three-day" or pappataci fever from dengue than the Calcutta seven-day fever. The latter may for the present be classed as sporadic dengue.

The generally acknowledged differences of the older descriptions of epidemic dengue and the sporadic disease now annually present in Calcutta may possibly be explained by a change of type brought about by the greatly increased rapidity and frequency of communication between tropical ports during the last fifty years. Thus in former times the infection of dengue was only introduced into Indian and other tropical and subtropical ports at considerable intervals, when it spread as an almost universal epidemic among the highly susceptible population. With much more frequent opportunities for the introduction of the infection a larger proportion of the population retain the immunity to the disease acquired by a previous attack, and the outbreaks become less and less widespread until eventually the disease becomes sporadic. This view is supported by the fact that the first cases each year in Calcutta are usually seen in sailors, due to an annual reintroduction of the disease from warmer, more southerly ports, where the temperature conditions allow of its continuing all the year round.

Practically every European who lives long in Calcutta suffers sooner or later from the sporadic seven-day type of fever, and the same is probably true of the three-day Punjab type in the areas in which it prevails. One attack generally confers immunity for several years, after which a second, and usually milder, one may be experienced. Previously, when not incorrectly returned as malaria, as was nearly always the case in Calcutta before I described the seven-day type, cases of dengue were classed as "ephemeral fever" and "simple continued fever," or since the introduction of that term into the official nomenclature, as "pyrexia of unknown origin," which is a great advance on incorrectly returning them as malaria.

For the above reasons I propose to class these fevers provisionally under dengue, and first describe the epidemic form as recorded by the older writers, then the sporadic seven-day fever type as now recognised from full notes of over two hundred cases I studied with blood examinations in the Calcutta European Hospital, and lastly deal with the three-day type, now usually known as pappataci fever. It should, however, be borne in mind that outbreaks of dengue of intermediate degree between the old nearly universal epidemics and the sporadic form now seen yearly in Calcutta have been described in recent years.

EPIDEMIC DENGUE

At variable intervals epidemics of dengue have spread widely in the East, attacking three-fourths or more of the entire population of large towns within a very few weeks, producing great dislocation of business, and then disappearing again, often for a number of years. According to Lichtenstern, the earliest reported outbreak was in 1779 at Java and in Egypt, and in the following year in Arabia and Persia; it also reached the United States of America. In 1824 another great wave started in the East, severely affecting India, spreading to Suez, and during the following four years extended over the greater portion of the tropical and subtropical zone. During the next four decades several slighter outbreaks occurred, the coast towns of India being attacked in 1830, 1835-36, 1844-47 and 1853-54. Another great epidemic appeared in 1871-73, this time originating at

Zanzibar in East Africa, spreading to the Arabian and Indian coasts, and also involving the East Indies and Southern China. In 1876 Hongkong was affected, the disease being also carried to Egypt, in the next few years it invaded parts of the Mediterranean coast, being very prevalent in Asia Minor and Turkey in 1889. In 1901 dengue appeared in Hongkong, was checked in the winter, but reappeared in the summer of 1902, and became prevalent in Singapore, Madras and Rangoon, and spread far inland into Upper Burma. As excellent descriptions of the great outbreaks of 1824, 1872 and 1902 in India are on record, I carefully studied the original publications, and have based on them the following description of the principal features of the disease. The most important statements are given as nearly as possible in the words of the authors named in the bibliography at the end of this chapter.

Prevalence.—The 1824 outbreak first appeared in Rangoon about the end of May and reached its height at the end of June. It appeared in Calcutta about the beginning of June and extended to Chittagong and Madras, and also widely inland throughout Bengal and the United Provinces, spreading mainly along the Ganges River. Guzerat, on the Bombay side, was also severely attacked in June 1824, few escaping. Thus, the disease was by no means confined to the coast, and spread very rapidly over the greater part of India.

Another characteristic feature is the exceedingly rapid spread through the population of affected places. Thus, in Calcutta in 1824 it is recorded that with very few exceptions it spared none of either sex or of any age, while Twining says that the earliest cases were seen on May 23, and in the course of ten days great numbers of persons were ill of the fever ; so that before the end of June nearly half the population of Calcutta had been affected, and eventually he estimated that not more than 200 out of the total inhabitants escaped. Throughout July the disease continued unabated, and towards the end of that month primary attacks were comparatively rare, there being few at that time who had escaped the fever ; no first attack was seen after August 11. In Guzerat very few indeed of the natives escaped, though Europeans were more fortunate : this is just the opposite to the regular incidence of seven-day fever (see p. 307).

In 1871 epidemic dengue reached Calcutta in October from Zanzibar, and continued to be prevalent throughout the cold season in the Hastings barracks, nearly every family, and in some cases every resident, being attacked. In April 1873 it increased again in Calcutta, and during the following month it continued as a widespread and universal epidemic in Calcutta, and extended over the whole country, affecting all parts of Bengal in June, reaching the United Provinces, Bombay, Madras and Burma provinces in July. In September it overran the Punjab and Central India, while in Aden 80 per cent of the population suffered, so that no province of India appears to have escaped the epidemic.

Much milder outbreaks of what was considered to be dengue were also described by H. H. Goodeve in 1844-45 and by Edward Goodeve in 1853. The account of the latter writer appears to me to more closely resemble seven-day fever than epidemic dengue, as only 28 cases were seen by Goodeve, two-thirds of which were in Europeans, nearly all sailors, although they occurred in the Medical College Hospital, where the great majority of the patients are natives, while it is recorded that "the present epidemic differed from

previous outbreaks of dengue in the absence of severe rheumatic pains." This may therefore have been only a year in which seven-day fever was unusually prevalent with the result that attention was attracted to it.

As recently as 1902 a severe outbreak of dengue affected Hongkong, Singapore, Madras and Rangoon, and from the latter place spread inland for about one thousand miles to Bhamo in Upper Burma. This outbreak is believed to have come originally from Hongkong. In Madras it was very widespread, while such was the infection in hospital that so many of the medical staff and nurses were attacked at the same time as quite to disorganize the working of the institution. It attacked all races and showed no preference for Europeans. Strange to say, Calcutta escaped this outbreak, cases of seven-day fever having been unusually few there that year.

Distribution.—In addition to the foregoing epidemics, outbreaks of dengue have been reported in recent years in the following countries : In India at Bombay on a naval vessel by Bassett-Smith ; at Nowshera in the Punjab in 1909 by Wimberley, the fever being noted to resemble McCarrison's three-day type, but with the unusual symptom of vomiting in a very large proportion of cases ; in Calcutta in 1909, of the seven-day type, among Indian troops by Campbell Munro, who noted that a regiment from the Punjab, where the three-day type of fever is widely prevalent, suffered much more severely than one from Madras, where dengue occurs—from which he argued that the Punjab three-day fever of McCarrison differs from dengue, and does not protect against it : a statement which is supported by F. Smith, who saw sporadic dengue in Indian troops in Calcutta from 1910 to 1912, and observed that a regiment which came from three-day-, sand-fly-, fever-infected United Provinces was severely attacked by dengue in Calcutta, where both the seven-day and three-day types of the latter disease were prevalent. Kennedy also described an outbreak of dengue in Indian troops in Calcutta in 1912, which spread rapidly in the regiment, but not in hospital, and he thought that it was carried by *culex fatigans*. Khan describes an outbreak at Meerut in the United Provinces in 1913 with 1400 cases. The disease is therefore liable to occur in most parts of India, always in the hot or rainy season ; it dies down in the autumn, just when malarial fevers increase.

Other parts of **Asia** to suffer from dengue are the Philippine Islands, as recorded by Ashburn and Craig in 1907 ; Indo-China, the disease having been reported by Legendre as endemic in Hanoi since 1910, while Gaide recorded its presence in that country as early as 1890, and between 1905 and 1908 four epidemics occurred, all commencing in the hot weather and terminating quickly at the first appearance of the cold season. In Formosa a disease has been described as dengue, but as the mortality was 14 per cent, the diagnosis seems open to doubt. In Asia Minor dengue was described at Beyrouth by Graham, who appears to have been the first to attribute the infection to culicides, and in Palestine at Jerusalem in October 1912 by Canaan, who considers that it differs from pappataci fever in the longer duration of the temperature and in attacking the older inhabitants.

In **Africa**, dengue has been recorded at Port Said by E. H. Ross, where the disease

declined greatly as a result of anti-mosquito measures, in Mauritius by Vinson as a sporadic disease in 1914, while Archibald reported on 300 cases seen in Western Sudan in 1917.

In **America** both Deeks and Perry described in 1912 six- and seven-day fevers resembling Rogers' Calcutta seven-day type, and Lavinder and Francis met with dengue in Georgia in the Southern States. King reports fully on dengue in Porto Rico, where in September 1915 a widespread epidemic of variable type occurred without any mortality. He found the pulse rate of little diagnostic value. Meagher met with an epidemic at Bermuda in the summer of 1915 which attacked about half the population.

In **Australia**, dengue was epidemic in 1905, attacking all but a small percentage of the population. In 1916 it broke out in New South Wales, where it was equally widespread, a relatively slow pulse having been noted in this outbreak, as in the sporadic disease in Calcutta. In Samoa, Poleck recorded an outbreak of six-day fever in 1912.

In **South-East Europe** the disease has been reported, but the cases resembled more closely pappataci or three-day fever than typical dengue.

Seasonal Incidence.—The above account of the prevalence of epidemic dengue in India shows that the hot weather and rains are the regular season for the occurrence of epidemics of the disease, although it was prevalent throughout the cold season in Calcutta in 1871-72.

Racial Incidence.—Epidemic dengue affects all races indiscriminately, and does not show the preference for newly arrived Europeans which is so marked a feature of the sporadic type.

CLINICAL DESCRIPTION OF EPIDEMIC DENGUE

Onset.—In the 1824 outbreak Mellis described the invasion as generally sudden, with chilliness and occasional rigors, lassitude and pains in the head and body and sometimes in the muscles and joints. O'Connell Raye in 1872 says it began without premonitory symptoms, or was preceded by slight malaise for a day or two, the onset being characterized by sudden acute pain in one or more joints, followed quickly or accompanied by chills, scarcely amounting to rigors, and after about six hours by burning fever, pains extending to every joint and bone and maddening headache.

Breakbone Pains and Joint Symptoms.—In both of the great Eastern epidemics the pains were the most characteristic symptom of dengue. Thus Mouat writes of the acute pain in all the joints, rendered excruciating on the slightest touch, and of universal soreness, rendering every position alike uneasy and intolerable. Twining describes severe pains in the loins, muscles of the limbs, an extreme degree of anxiety and jactitation, the suffering from pain being a leading feature of the disease. Raye in 1872 records that "in all cases pain of greater or less severity is present. In the great majority it is the most urgent and distressing symptom, the earliest harbinger, the persistent companion, and the last vestige of the disease." Usually it is acute and sudden and may attack but one joint. With it there is racking headache, maddening pain in the back, as if it was being broken in two, or as if the body had been beaten with sticks, while, when apparently

recovering, stiffness and soreness of the joints may return with redoubled energy, producing crippling of the patient. Again, Edmonstone Charles wrote that "in more than half of the cases of dengue I have seen this pain of the joints has been a symptom so well marked as to distinguish it from all other eruptive fevers," and he considered pain in the small joints as almost pathognomonic of dengue, although they may be absent in some cases.

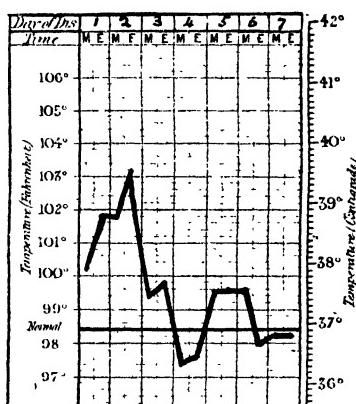
After Joint Pains may last for long during convalescence from the fever, and produce the stiffness and crippling from which the name of dengue, or "dandy fever," is said to have been derived. Thus, Mellis, writing after the 1824 outbreak, refers to the continued pains in several joints, large and small, sometimes in one finger only, so that at the time he wrote there were many whose limbs have been considerably paralysed, and the smaller joints so benumbed as to render them incapable of being used freely. Twining remarks that protracted debility, long-continued pains in the ankles, and dull aching pains in the joints of the fingers and toes were almost invariably complained of for many weeks after the cessation of the fever. In 1872 Raye records that the joints ache for days or weeks after the cessation of the fever, and E. Charles says that the aching may last for a day or two, or pass off in a week or ten days, but is often much more persistent than this, and lasts for six weeks or three months. W. G. Pridmore, I.M.S., also noted pains, swelling and tenderness of the joints in the Bhamo outbreak in 1902.

Convalescence is also often very slow, Kennedy in Guzerat saying that few recovered under three months from the debility and aching pains in the wrist and ankles which the disease left behind it; while Twining remarks that "although the most urgent febrile symptoms for the most part remitted in less than two days, I believe few were so fortunate as to pronounce themselves quite well in a month."

Duration of Fever and Temperature Curve.—

One of the most commonly used symptoms for dengue is "three-day fever," a term which occurs both in the older Indian writings and in Lichtenstern's account in *Nothnagel's Encyclopedia of Medicine*. It is certainly a correct designation as far as the great Indian outbreaks of 1824 and 1872 are concerned. Thus, Kennedy observed that the third day was decidedly critical; Cavell found that in thirty-six hours the fevers almost always subsided and the patient was in a state of convalescence; and Twining wrote of the remission of the pyrexia after the second day. Of the 1872 outbreak temperature charts are available, and a series published by Raye shows the temperature rising rapidly during the first twenty-four hours to from 103° to 105° , and then falling quickly on the second or third day to the normal standard, or usually below it, 96° being common after

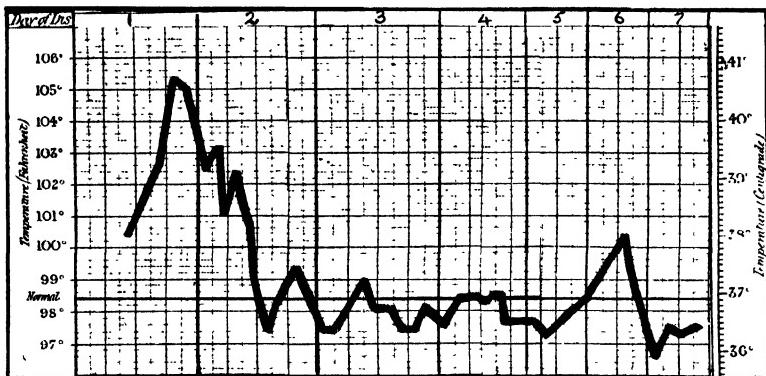
CHART 56



Ordinary type of dengue
(Edmonstone Charles).

the paroxysm has passed away. "For the rest of the attack the temperature rarely rises above the normal standard, unless for some accidental cause." Of seven charts

CHART 57

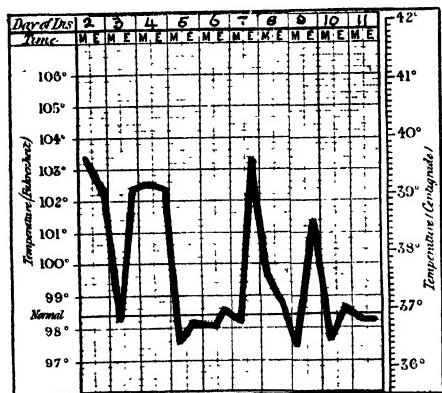


Dengue, three-hourly chart showing remittent type of fever and slight secondary rise on the sixth day (Edmonstone Charles).

published by him, in one the fever lasted one day, in five for two days, and one for two and a half days. In only one was there a very ephemeral secondary rise to 100° F. Edmonstone Charles remarked that the febrile stage of dengue is one of the most constant features of the disease,

and he described it as follows: "In general terms the highest temperature occurs about twenty-four hours after the seizure, while before twenty-four hours more have expired, the whole of the pyrexia is at an end. Such a complete crisis may be delayed for a day." He gives Chart 56 to illustrate the ordinary course of the fever. He also states that the fever is distinctly remittent in character, varying rapidly, so that three or four well-marked alternations of temperature may occur in the course of twenty-four hours, as in Chart 57, which he gives to illustrate this point. Under the head of relapses, he mentions that occasionally a slight rise of

CHART 58



Dengue, severe relapsing type (Edmonstone Charles).

temperature to about 100° F., as in Chart 57, may take place from the fourth to the sixth day, but this is exceptional. In rare cases it may be more marked, as in Chart 58, which he gives as that of a severe relapsing dengue, remarking that these cases are far from common. The marked intermissions of temperature are noteworthy here, as

they present a great contrast to the prolonged continued terminal rise of seven-day fever as shown in Chart 66 and pages 300, 301. W. G. Pridmore in the 1902 outbreak in Burma records that the fever "remains high with slight remissions for one, two or rarely three days, and then falls rapidly." A secondary rash was almost invariably present on the sixth day and was "never accompanied by more than a trifling rise of temperature." Stedman's account of the Hongkong outbreak agrees very closely with Pridmore's statement.

These accounts of the temperature curve in dengue are in entire agreement with those of Lichtenstern and Sir Patrick Manson. The former describes the dengue as a "three-day fever," terminating usually by crisis followed by a subfebrile stage with a secondary rash, and then convalescence without any second rise of temperature, but leaving extreme debility. The latter describes the fever as lasting from one to three or four days, and terminating in the vast majority of cases by falling abruptly to below the normal line about the end of the second day by crisis of diaphoresis, diuresis or epistaxis. From the fourth to the seventh day there is commonly a terminal rise of but a few hours' duration reaching to 103° F.

Rashes.—In the early stage there is often a primary red erythematous rash over the face and sometimes on the extremities, but rarely, according to Raye, on the abdomen. It fades with the decline of the temperature. A secondary rash of a papular nature appears usually on the fifth or sixth day, without any rise of temperature (Raye and E. Charles). It is best marked on the arms and chest, but is usually also seen on the body and legs, and may affect the face, although less markedly than in measles, which it otherwise closely resembles in its general character. It is often of very short duration, and usually fades after about twenty-four hours. E. Charles states that it may be urticarial in nature, and that it was absent or overlooked in about one-third of his cases. The occurrence of this rash in the absence of fever, he thinks, differentiates this disease from all other exanthemata. E. Charles never saw any desquamation, but Mouat mentions a scurf-like, or branny, exfoliation.

Relapses.—Another feature of dengue is the frequency of relapses within a short time of the primary attack, and in the same season. Thus Twining observes that "many suffered from relapses nearly equal in severity to the first attack, and third attacks have been seen." Kennedy says two attacks may occur in one month, and Raye saw them two to four weeks after the primary attack.

The Pulse in dengue is almost universally described as being very rapid. Mellis found it to beat 30 to 40 strokes above the normal, while the increase was sometimes much greater; Twining says it soon becomes remarkably frequent, being over 100 in most cases within six hours of the attack, and often more rapid, in one case reaching 140; Raye says it rises to 110 to 115 most usually, but 130 is not at all uncommon; and E. Charles says that, although the pulse may be under 100, a very common rate is 108, while it only exceptionally rises above 120, although it may reach 140.

The Tongue is usually described as furred in the centre with red edges, and sometimes with red papillae on the dorsum. The **throat** may be slightly congested, but rarely presents any prominent symptoms. A disposition to vomit is mentioned by one writer,

but sickness appears to be a rare symptom. Catarrhal signs in the lungs are only mentioned by two writers, these organs not usually showing any changes.

Blood Changes.—These do not appear to have been very closely studied. Stitt in the Philippine Islands found a leucopenia, with a decrease of the polynuclears, and great variation in the proportions of the different mononuclears. The lymphocytes were first increased, and later the large mononuclears. Andrew Balfour found similar changes in a few Egyptian cases. Graham of Beyrouth has described an unpigmented amoeboid parasite in the red corpuscles. His observations still lack confirmation.

Diagnosis.—During the primary rash dengue may be mistaken for scarlatina, some of the cases attributed to that disease in tropical places having been possibly really dengue. During the terminal rash it may resemble measles, but the absence of fever will generally serve to distinguish it.

SPORADIC DENGUE (SEVEN-DAY FEVER OF CALCUTTA)

Clinical Description.—The onset of the disease is almost invariably quite sudden. In 60 per cent rigor or chilliness occurred at the commencement of the fever, but in nearly 40 per cent this symptom was absent. In 15 per cent a history of repeated rigors was obtained, usually in cases admitted late in the disease, and in such cases malaria is specially closely simulated, a suspicion which becomes strengthened by the early cessation of the fever while taking the inevitable quinine. Only rarely is the onset described as being gradual, as in typhoid fever.

Appearance on Admission.—In patients coming under observation in the earlier stages, the following appearances may be noted. The face is usually flushed and the palpebral conjunctiva presents a vivid red coloration, best seen on turning down the lower eyelid. The general expression is often dull and listless, being highly suggestive of early typhoid, while in some cases the addition of slight abdominal pain or distension, and even a few rose spots, gave rise to such a strong suspicion of that disease, that a Widal test was performed with a negative result, which was soon confirmed by the early cessation of the fever about the seventh day. I have also been repeatedly called into consultation to do a Widal test, the patients in several instances being relatives of doctors, but after some experience could almost always correctly suspect the true nature of the case from the history and a clinical examination.

Pains in the Back and Limbs.—Another very early and constant symptom is pain in the back, and only slightly less frequently in the limbs as well, while pains were often complained of as being all over the body. Eighty per cent of the cases came under one of these headings, while in only 4 per cent were pains recorded as being absent. In only 7 per cent were they noted as affecting the joints, and in none of these was there any swelling, redness or tenderness locally, while in only one case were the bones specially mentioned as being involved.

Headache.—Another very constant and distressing symptom is headache, almost invariably frontal in site, and frequently affecting the back of the eyes. When the patient

is asked to indicate the exact position of the pain he generally places his forefinger and thumb one on each side just behind the external orbital processes of the frontal bone. The headache in malaria is less frequent and severe, and more variable in position than that of seven-day fever.

Alimentary System.—The tongue also has a characteristic appearance, namely, marked furring of the dorsum with red raw edges and sometimes even a strawberry appearance. This condition differs widely from the uniform slight furring in malarial fevers, but resembles that of influenza and dengue.

Sickness was noted in one-fourth of the cases and nausea in 18 per cent more, so that in the majority of them there was no gastric disturbance, which is, therefore, much less common in seven-day fever than in malaria, where it is specially frequent in the malignant tertian form, which is just that variety most likely to be confused with seven-day fever.

The Bowels were regular in half the cases, constipated in one-fourth, while there was diarrhoea or irregularity in the remaining fourth, although it was seldom at all severe.

The Abdomen was not infrequently either somewhat distended or the seat of pain; more so, indeed, than in any other class of fever except typhoid itself. During the second year's observation, when fuller notes were kept than in the previous year, some degree of distension of the abdomen was recorded in one-fifth of the cases admitted in an early stage, while it was the seat of pain in nearly as many more, so that in one-third of the total some abdominal symptoms were present. Further, in 5 cases suspicious rose spots were observed on the abdominal or thoracic wall. These points are of special importance in view of the frequent confusion between the more continued type of seven-day fever and the early stage of typhoid, and also in co-relationship to the organism I have cultivated from the blood of seven-day fevers which is nearly related to the great typhocoli group of organisms.

The Liver was slightly enlarged in only 5 per cent of the cases, and never extended more than 1 in. below the ribs. It is probable that any series of men in the tropics would furnish such a small percentage of slightly enlarged livers, while no symptoms referable to this organ have been met with in seven-day fever.

The Spleen was very rarely enlarged in seven-day fever, being felt below the ribs usually only during deep inspiration, in but 7 per cent of the total cases, and in the second year's series in only 2 per cent. In only 1 case was the enlargement at all marked, and this was probably independent of the present attack of fever. In this respect seven-day fever differs markedly from malaria, for in the latter disease the spleen was found to be enlarged in nearly half the cases.

The Respiratory System.—Symptoms referable to the respiratory tract were also conspicuously absent. Out of a little over 200 cases in only 3 was any coryza recorded, and in one of these it had been present some time before the fever began. In 4 more slight congestion of the throat was noted. The lungs were nearly always free from physical signs, a slight degree of bronchitis being detected in only 4 per cent and in addition slight consolidation at the base in one. The escape of the respiratory tract is of great value in

separating this disease from influenza, which it so closely simulates in its sudden onset with pains and aches all over. In the 1892 outbreak of influenza in Calcutta, at any rate, throat and lung symptoms were very constantly present, while the seasonal incidence was quite different from that of seven-day fever (see p. 382).

Circulatory System.—No cardiac complications have been noted in seven-day fever; in this respect the disease again differs from influenza with its frequent late cardiac affections.

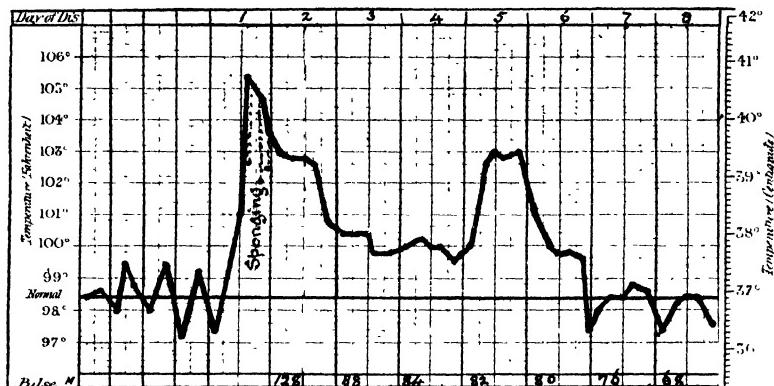
The Pulse, however, presents a very important feature, for a most constant and characteristic slowness in proportion to the temperature is found, just as occurs in typhoid and paratyphoid. At the very beginning of seven-day fever the pulse may occasionally be fairly rapid, reaching over 100 beats a minute, but once the patient has been placed at rest in bed it rarely if ever rises above that frequency. During the high terminal rise of temperature it scarcely ever exceeds 100, being more commonly about 80 to 90 only, while after the temperature finally falls to normal it may be 60 or less. The great practical importance of this feature is that it nearly always allows of the difficult cases, admitted only during the terminal rise of temperature, being readily differentiated clinically from malaria, with which they have hitherto been almost invariably confused. In malaria, during a pyrexia of 103° F. or more, the pulse is nearly always over 100 a minute, and usually rises to 110 or over (see p. 240).

Cutaneous System.—Rashes are occasionally seen in this disease, but were only found in quite a small proportion even of the cases coming under observation in an early stage of the fever. Out of the total number a rash was recorded in only 7 per cent. It was usually of a mottled character, and most frequently seen over the extensor surfaces of the forearms, but in a few cases was so extensive as to lead to a diagnosis of measles being made. This rash almost always appeared from the fourth to the sixth day of the disease, being thus a late manifestation, although only present during the course of the fever, and not after its fall, as in the much more constant rash of true dengue. I think that 7 per cent is rather an underestimate of its frequency, as it may sometimes be of short duration and so not be recorded, but even allowing for this, it was quite an exceptional symptom in both years' outbreaks. No marked desquamation follows it, and it usually fades before the temperature falls.

The Temperature Curve.—The course of the fever varies very much in accordance with the stage of the fever at which the patient comes under observation, so that it was only through careful watching of a long series that I was able to recognize that the different types seen were but variations of a single disease, and so to separate it from "abortive typhoid" and "simple continued fever," so called, on the one hand, and from malaria on the other, these being the terms under which the cases have hitherto been almost invariably returned in the different parts of India where this fever occurs. Nevertheless, the fever has a most characteristic temperature curve, best described by the term "saddle-back," which it will be well to illustrate first, and then to return to the variations from this typical course.

The Typical Saddle-back Temperature Curve.—Chart 59 shows the characteristic temperature curve from beginning to end. The temperature, which was taken every four hours, rose rapidly to over 105° F., and was very little reduced by repeated spongings

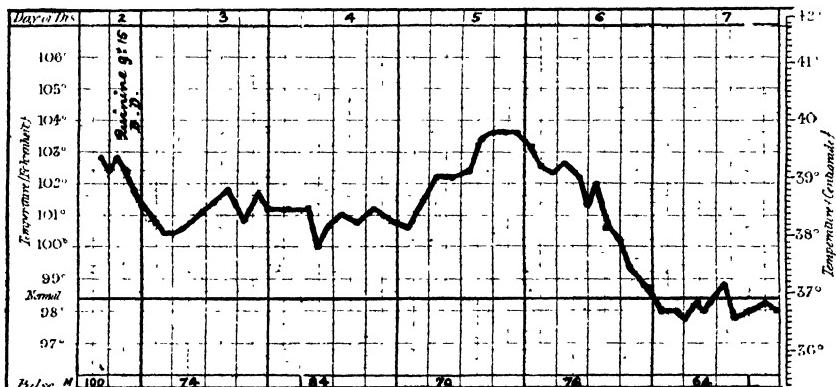
CHART 59 (Case 1195)



Seven-day fever, showing typical saddle-back temperature curve.

(as shown by the dotted lines in the chart). It gradually declined during the next two days to about 100° F., at which point it remained steadily for three days before the characteristic terminal rise carried it up again to 103° F.; this was succeeded by the

CHART 60 (Case 1031)



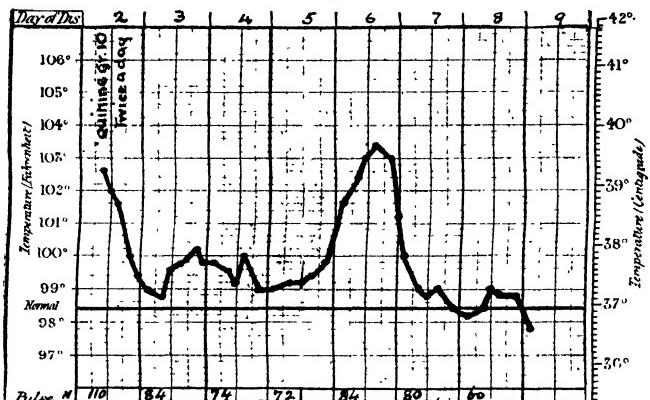
Two-hourly chart, showing continued type of fever with slow pulse.

final fall occupying twenty-four hours. The pulse was markedly accelerated during the unusually high first rise of the temperature, but during the terminal one it is noteworthy that it was not found to reach over 82 beats a minute, with a pyrexia of 103° F.

FEVERS IN THE TROPICS

Chart 60 is a two-hour curve showing how continued the fever was between 100° and 102° F. before the typical terminal rise. The pulse in this case was never recorded

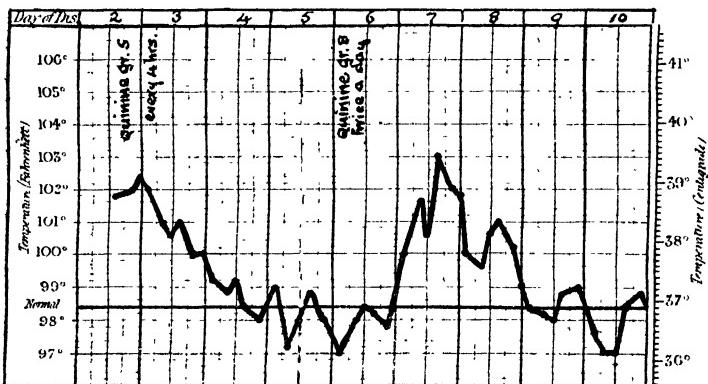
CHART 61 (Case 163)



Seven-day fever, showing deep saddle-back remission.

as above 100, and never reached even 80 during the terminal rise, in spite of the temperature attaining to over 103° F.—a most characteristic feature of this fever. In fact, up to the sixth day the pulse and temperature curve might have been those of typhoid, except that

CHART 62 (Case 783)



Seven-day fever, with complete remission to normal before terminal rise.

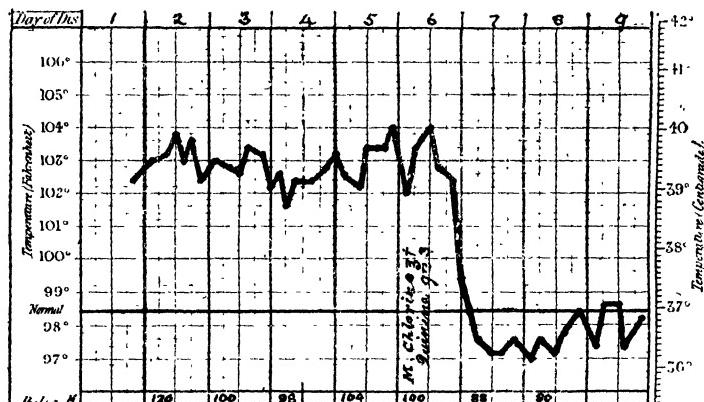
in my experience such a saddle-back remission to as low a point as 100° F. is rare in the early stage of typhoid once a higher point has been reached.

Chart 61 again shows the same saddle-back type, but with a still more marked remission to 99° F., and a final rise once more to 103° F., accompanied by a pulse not exceeding 100 per minute, except immediately after admission.

One step more to a complete remission of the temperature to the normal point, and we arrive at Chart 62, in which the pyrexia ceased for two complete days, and yet the terminal rise to 103° F. occurred before the final fall to normal. Such a complete remission as this is exceptional, for in five-sixths of my cases, patients admitted within the first few days, the temperature never fell below 99° F. during the usual remission, while in fewer still did it actually reach the normal line, a point in which this seven-day fever differs most essentially from the three-day pyrexia ending by crisis of true epidemic dengue.

Continued Typhoid-like Group.—Although the saddle-back temperature curve is by far the most characteristic and usual type in patients admitted in the early days of the fever, still there may be considerable variations from this form, the most important of which is the continued type simulating the early stages of typhoid, for the latter disease

CHART 63 (Case 213)



Seven-day fever, showing high continued type resembling typhoid.

by no means uncommonly begins fairly abruptly and without the classical step-like rise in tropical India. Chart 63 is one of the most marked examples of this form I have met with, although I have a number of charts showing an equally continued fever, but usually at a slightly lower level. These continued cases frequently give rise to groundless fear of typhoid, but the symptoms already described will, as a rule, allow of a correct diagnosis being arrived at after some experience of the disease. In several private cases in which I was asked to examine the blood for typhoid I have been able to recognize the new fever clinically, and correctly to assure the friends that the temperature would fall on the sixth or seventh day.

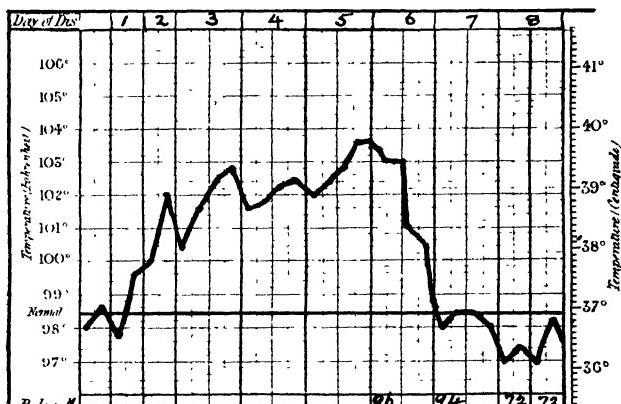
Chart 64 is that of another patient, attacked while in hospital, in which the high initial rise is less abrupt than usual, so that the terminal one shows the highest point of the pyrexia, but with a slow pulse—a less uncommon type which may also give rise to a suspicion of typhoid for several days.

Chart 65 illustrates the opposite condition, also quite exceptional, in which the

terminal rise is completely absent, although the temperature did not finally reach the normal until the sixth day.

Terminal Cases.—I have already mentioned that just about half these patients only come to hospital during the terminal rise of temperature, and this is easy to understand

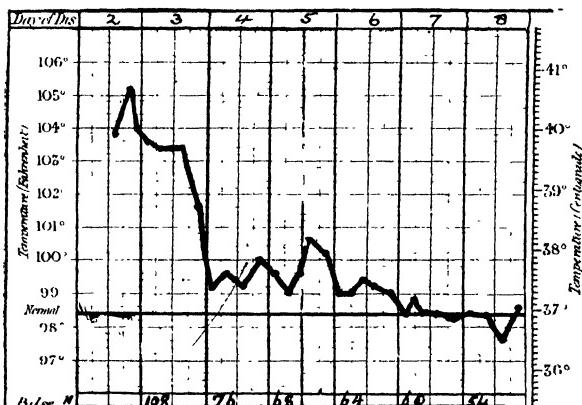
CHART 64 (Case 311)



Seven-day fever, with absence of remission and resembling the commencement of typhoid.

when we remember that in a large number of the cases the pyrexia falls to about 100°, or under, on the second or third day, accompanied by a remission of the severe headache and

CHART 65 (Case 294)

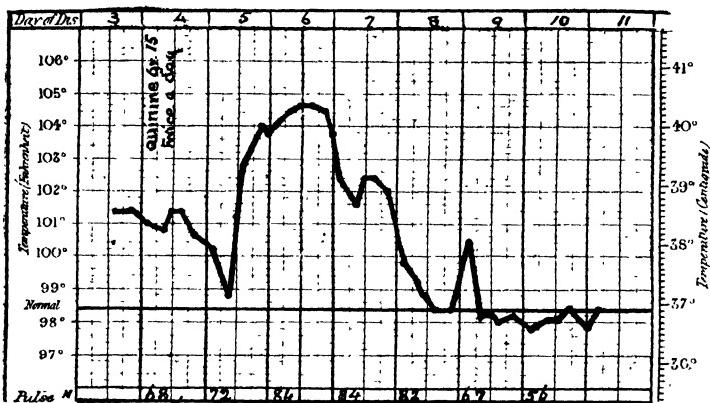


Seven-day fever, with absence of terminal rise.

pains in the back and limbs, so that the patient thinks he is rapidly getting over his trouble. It is only when he is rudely awakened from this happy frame of mind by the second rise

of temperature that he comes into hospital for treatment. There his fever rapidly ceases while taking the inevitable quinine, so that both he and his doctor usually have no suspicion that he has suffered from anything but an attack of malaria.

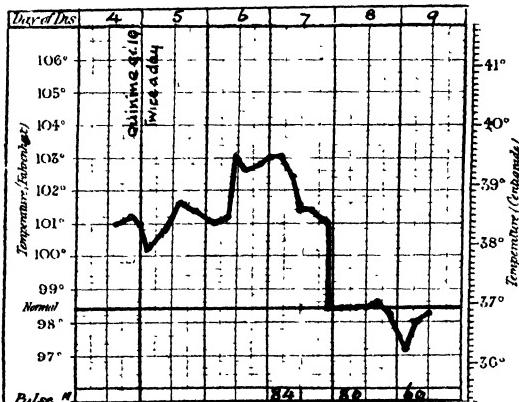
CHART 66 (Case 1147)



Seven-day fever, showing prolonged high terminal rise with slow pulse.

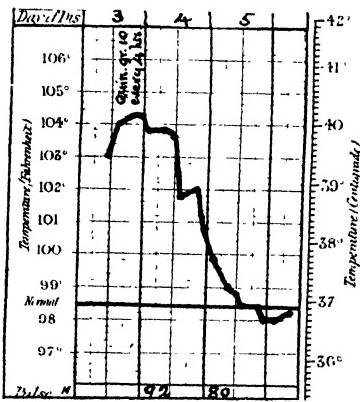
Chart 66 is that of a patient admitted on the third day, in which the temperature fell almost to normal on the following day, after which a well-marked terminal rise took place,

CHART 67 (Case 376)



Seven-day fever, admitted on fourth day, showing terminal rise with slow pulse.

CHART 68 (Case 568)



Seven-day fever, admitted about the beginning of the terminal rise.

during which the temperature remained persistently at about 104° F. for over twenty-four hours in spite of frequent sponging, which had only a very ephemeral effect on the pyrexia. The pulse was never recorded as rising over 92 during this high temperature,

while a very slight and short recrudescence of fever occurred just after the cessation of the secondary curve, as is occasionally the case.

Chart 67 is that of a man admitted on the fourth day with a low continued type of fever succeeded by the characteristic terminal rise with a slow pulse.

Chart 68 is that of an unusually short case admitted at about the beginning of the terminal rise, the fever only lasting two days under quinine, but with the slow pulse of seven-day fever and not the rapid one of malaria. In this case, *as in every one on which this description is based*, a blood-film, taken before any quinine had been administered in hospital, was examined by me for malarial parasites, with a negative result.

The last three charts will serve to illustrate the very frequent cases admitted during the terminal rise of pyrexia, many of them only coming to hospital on the fifth or sixth day of the disease, but a few hours before the final fall. In such only the history of the patient, the absence of malarial parasites, and above all the slow pulse during high fever, aided by their occurring in the regular season for this disease, will allow of a correct diagnosis being arrived at, and the common error of returning them as malaria to be avoided. Megaw describes the following types : (1) Evanescent, with so short a rise of temperature that it may be overlooked. (2) The short type as in three-day fever of Chitral, with temperature for from thirty-six to eighty-four hours. (3) The interrupted type, like the last but with a second rise of temperature of one or two days' duration beginning on the fifth or sixth day. (4) The saddle-back type described by Rogers. (5) The continued type.

THE DURATION OF THE FEVER

On account of the patients coming to hospital in any stage of the disease, the actual duration of the fever after admission varies widely from one to eight, or rarely slightly over eight, days. The total duration of the fever in just about three-quarters of them was either six or seven days, so that the temperature either fell to normal on, or finally remained normal during the seventh day in this proportion, and hence the name of "seven-day fever," which I have proposed for the disease. A slightly larger number of cases end on the sixth than on the seventh day, but it appeared to be better to take the latter day for the name of the affection so as not to lead to its termination being expected at an earlier date than actually occurs in almost half the total cases. Table XXXIV. shows the number of cases which terminated on different days of the fever, the cases denoted "typical" being those admitted sufficiently early to show the characteristic saddle-back or complete terminal rises of temperature, while the "terminal" cases are those admitted near the end of the disease, and so especially liable to be returned as malarial.

TABLE XXXIV.—DURATION OF THE PYREXIA IN SEVEN-DAY FEVER

	-3 Days.	3 Days.	4 Days.	5 Days.	6 Days.	6 or 7 Days.	7 Days.	8 Days.	+8 Days.	Total.
Typical cases .	0	0	3	5	39	(76)	37	8	8	100
Terminal cases	0	4	5	10	40	(69)	29	10	8	106
Total cases .	0	4	8	15	79	(145)	66	18	16	206

It will be seen from this table that in no case did the fever last less than three days, while in only 4, or 2 per cent, did it end on the third day, all these being terminal cases in which the history of the duration of the fever before admission may have been inaccurately given. Further, only 8 cases, or 4 per cent, ended on the fourth day, so that in the remaining 94 per cent the fever lasted five or more days ; and in 86 per cent it lasted six or more days—a point of the utmost importance in separating this disease from true epidemic dengue with three or less days' fever, according to the great majority of experienced writers on that disease. As I was examining the blood of every fever case in the hospital it is impossible that I could have overlooked an appreciable number of short cases of this fever, for exceedingly few such cases without malarial parasites in their blood occurred during the months when the seven-day fever was prevalent.

Convalescence.—Once the temperature is normal and the patient up and on full diet, convalescence is very rapid after seven-day fever, as was pointed out by Dr. J. G. Murray, I.M.S., at the recent debate in Calcutta already mentioned, this officer having had a very large experience of the disease in his wards at the European Hospital. He also stated that he had never seen a case of three or less days' duration, nor the very severe pains and joint complications of true dengue ; moreover, the pains did not return during the terminal rise of seven-day fever as in dengue. He regarded the slow pulse of seven-day fever as a characteristic point of difference from the latter disease.

Another important feature in the convalescence of seven-day fever is the absence of the chronic joint pains which are often so prolonged and distressing after true dengue, and which cause the crippling of the patient from which the name of the affection is said to be derived. These, on the other hand, I have never seen in the Calcutta sporadic seven-day fever.

Relapses.—I have not yet met with a case of seven-day fever which has relapsed during the same year as the primary attack, although the same person may rarely suffer from the disease again in a subsequent year if he remains in Calcutta ; but the fever is then usually in a milder form with a more marked and prolonged remission. This was well illustrated by the charts of two attacks experienced and recorded by J. W. D. Megaw, I.M.S., in a paper in which he ably advocates the view that the seven-day fever is but a sporadic form of dengue. In the latter disease, however, even repeated relapses during a single season are very common in Indian outbreaks.

THE BLOOD CHANGES IN SEVEN-DAY FEVER

Blood slides taken on admission before the administration of any quinine in hospital have been examined by me for malarial parasites in every case with invariably negative results. Further, no trace has been met with of the supposed protozoal parasite described by Graham in dengue cases seen in Beyrouth.

Total counts of the red and white corpuscles were made in a few cases, and showed an occasional slight reduction of the red, but a much more marked one of the leucocytes, which commonly numbered only from 2000 to 4000 per cubic millimetre, being thus

disproportionally reduced as compared with the red, so that the ratio was usually below 1 white to 1000 red corpuscles.

The Differential Leucocyte Count.—In 80 cases a differential leucocyte count was made from the blood films prepared on admission, the results of which are shown in Table XXXV., so to enable them to be readily compared with those of malarial cases in Table XXXIII. p. 254. The most essential feature of the leucocyte changes in seven-day fever

TABLE XXXV.—DIFFERENTIAL LEUCOCYTE COUNTS IN SEVEN-DAY FEVER

	Day of Disease		Temperature when blood was taken.			
	1-3 days.	+3 days.	-102.	+102.	Total.	Percentage.
Large Mononuclears.						
0-8	12	19	10	21	31	38.7
+ 8-12	10	12	10	12	22	27.5
+ 12-15	1	9	4	6	10	12.5
+ 15	8	9	11	6	17	20.2
Total	31	49	35	45	80	
Lymphocytes.						
-30	13	22	12	23	35	43.7
30-40	14	12	12	14	26	32.5
40	4	15	11	8	19	23.7
Total	31	49	35	45	80	

is a considerable reduction in the percentage of the polynuclears with a corresponding increase in those of the lymphocytes and large mononuclears. As the total number of leucocytes is also much reduced, the actual numbers of the lymphocytes and large mononuclears are not much if at all greater than normal, so that they are only relatively increased in proportion to the polynuclears, while the polynuclears are both relatively and still more actually reduced.

As an increase in the percentage of the large mononuclears has been regarded as a sign of the presence of malarial infection, the frequency and degree of this change in seven-day fever is of much importance. The increased proportion of the lymphocytes is also of interest in comparison with that of typhoid, which seven-day fever may resemble for a time. I have analysed the cases both as regards the duration of the fever and the height of the temperature at the time the blood was examined. The results show, in the first place, that the increased proportion of both the large mononuclears and the lymphocytes is more marked after the third day of the fever than during the first three days. Secondly, both these changes are considerably more marked when the temperature is normal or below 102° F. than when it is at a height of 102° or over. Of the 80 cases 39 per cent showed normal counts of 8 per cent or less large mononuclears, while one-third gave counts of over 12 per cent, and as many as 20 per cent showed over 15 per cent of large mono-

nuclears : the figure which Stephens and Christophers considered to indicate recent malarial infection. If only the cases are taken in which the blood was examined when the temperature was below 102°, then as many as 31 per cent of the cases gave over 15 per cent of large mononuclears. It is clear, then, that this test is of no value in differentiating seven-day fever from malaria, and it follows that in places where the former disease occurs *a large mononuclear increase cannot be safely regarded as evidence of malarial infection, a statement which is also true of kala-azar* (see p. 42). In fact, I was misled into recording as malarial remittents in a paper in Vol. 86 of the *Medico-Chirurgical Transactions*, two cases of what I now recognize to have been seven-day fever, by finding a marked large mononuclear increase in them.

The Lymphocytes were normal in 43 per cent, increased to between 30 and 40 per cent in 32 and numbered over 40 per cent in the remaining 23 per cent of the cases, while in cases with a temperature of under 102° this marked increase of the lymphocytes was met with in 31 per cent. In this respect the blood of seven-day fever closely resembles that of typhoid, although the additional increase of the large mononuclears is very rare in the early stages of typhoid, with which the seven-day fever can alone be confused on account of its short duration.

The Eosinophiles have been found by Harnett to be increased during convalescence.

It will be seen from the foregoing remarks that the leucocyte changes in seven-day fever are most variable, and afford little help in separating this fever from malaria or the early stages of enteric, with which it has been most confused. Moreover, in the presence of this fever the differential leucocyte count loses much of its diagnostic value in both malaria and typhoid, so that as a result of several hundred counts in all forms of fever in the East I have been reluctantly compelled to come to the conclusion that this method will not serve for the separation of the several fevers met with in the tropics, as I had hoped it might do, although it possesses considerable value in certain cases, and especially in the differentiation of early kala-azar from typhoid (see p. 132).

THE CULTIVATION OF A BACILLUS FROM THE BLOOD OF SEVEN-DAY FEVER CASES

Being struck with the resemblance of the more continued type of the seven-day fever, with its slow pulse, to typhoid and paratyphoid fevers, I made numerous attempts to cultivate a bacillus from the vein blood. An organism was thus obtained in pure culture in six cases during the two seasons' work, which appears to present constant features differing from those of the bacilli of typhoid and paratyphoid infections. The following are its principal characteristics.

In shape and size it resembles those of the coli group, and like them is actively motile ; flagella, in comparatively small numbers, having been demonstrated in some of them by my assistant, Dr. G. C. Chatterjee, to whom I am indebted for much help in testing the cultural characters of the organism. It is decolorized by Gram's method of staining, grows in broth with the production of a diffuse haziness, forms a thin film on gelatine at 70° F. without liquefying the medium, and shows much the same appearance as that

produced by the *coli* group on the surface of an agar tube. In a stab culture of glucose agar it does not grow very readily, except in the upper part of the streak and on the surface, and does not produce any gas-formation. On potato it forms an invisible growth like the typhoid bacillus. In litmus milk no clotting is produced, and only slight acidity results after a few days. In dextrose, laevulose, glucose, and maltose broths there is neither acid nor gas-formation, but with mannite slight acid-formation takes place after several days.

Dr. G. Dean kindly tested two of the organisms at the Lister Institute with the following additional results. No fermentation was produced at the end of twenty-four and forty-eight hours in arabinose, galactose, saccharose, lactose, inulin, salicin, erythrone, mannite or dulcite. He obtained slow liquefaction of gelatine. The organisms were on the average rather longer than the typhoid bacillus, with occasional long forms. They were distinctly motile, with an undulatory movement of the longer forms. He concludes that they do not give the reactions of any pathogenic bacillus known to him, though occasionally organisms are met with in faeces having these reactions.

The organism thus appears to be related to the great *coli* group, but differs from the organisms of typhoid and paratyphoid fevers. In addition to the cases in which it was isolated from the blood, a number of other cases yielded negative results, so that repeated examinations are necessary in order to obtain it, but this is, perhaps, not surprising in such a mild and short fever as the seven-day one is. Clumping was obtained with the organisms when mixed with the blood of patients suffering from seven-day fever, up to dilutions of 1 in 20 and 1 in 40, although the reaction was not sufficiently constant to furnish a reliable diagnostic measure, the fever apparently being too short in duration to yield much agglutinin. The only confirmation of the above work is that in Rangoon a similar organism was cultivated from the blood of several cases of seven-day fever. If, however, seven-day fever is only a sporadic form of dengue the proof that the virus of the latter can pass through a fine porcelain filter is much against any bacterial causation. Possibly some of the more continued cases I have described as seven-day fever may be a new mild short form of paratyphoid due to the above-mentioned organism.

Treatment.—Quinine is useless, and tends to aggravate the headache, while I know of no drug which influences the course of the fever, although salicylate of soda is useful in modifying the pains, and belladonna is worth trying if they are unusually severe. Aspirin and massage are also recommended by Megaw for joint pains.

The Mortality is usually nil except in very feeble subjects. Goldsmid, however, in New South Wales, met with three cases complicated with severe purpura, one of which, a child, died. Megaw states that fatal hyperpyrexia may occur in children.

Race and Sex Incidence.—The most striking fact in the incidence of the disease is that for the first month or two of its prevalence each year practically every patient is a sailor or some one connected with shipping on the river Hugli. Later in the season patients are admitted from other sections of the community all over Calcutta, but it especially affects newcomers rather than those who have lived for some years in the town. For this reason comparatively few cases were seen in females, and extremely few in children,

almost all the women and children admitted to this hospital belonging to the classes who are born and bred in India.

Among the native classes admitted to the Medical College Hospital cases are also occasionally seen, but this fever is many times rarer in the indigenous population than among Europeans, especially if the proportions of the two living in Calcutta are taken into consideration—another point in which it is at total variance with epidemic dengue.

THE SEASONAL INCIDENCE OF SEVEN-DAY FEVER COMPARED WITH THAT OF MALARIA

The monthly incidence of seven-day fever and malaria respectively during the two years that I microscoped the blood of every case is shown in Diagram V. In 1904 the

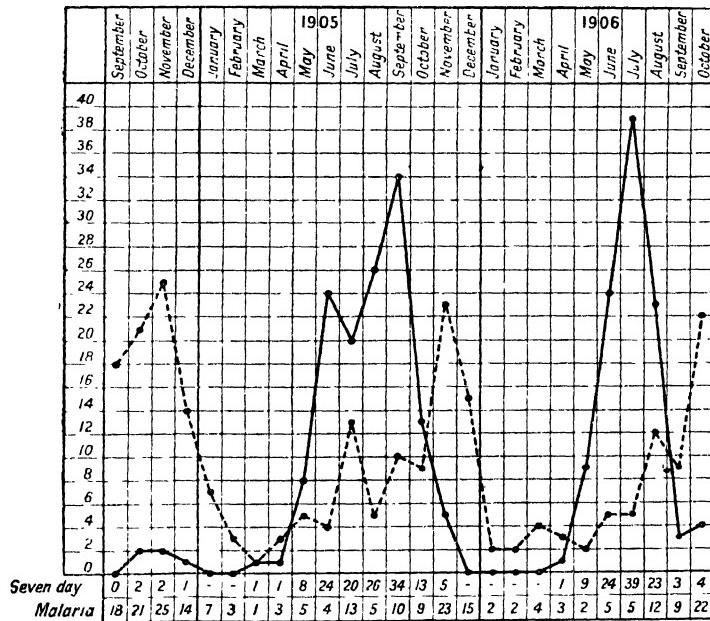


DIAGRAM V.—Monthly incidence of seven-day and malarial fevers in Calcutta.
Continued line = seven-day fever. Dotted line = malarial fever.

seven-day fever was prevalent from June to August, disappearing again in September, which is the very month during which malarial cases rapidly increased from a previous low level. The former remained practically absent from September 1904 to the following April. In 1905 the seven-day fever was unusually prevalent, beginning to increase as early as May and being very numerous from June to September, but rapidly declining during October and November, and disappearing once more from December to the following

April. Owing to a late rainy season the usual autumnal increase of malaria did not appear until November and December, when the seven-day cases had markedly decreased. In 1906 the new fever cases were less numerous than in 1905, but they began to increase in May, reaching the highest point in July and declining again to very few in September, the fall, as usual, taking place just before the main rise in the malarial curve.

If, however, a curve of the incidence of both fevers together is worked out (as shown in a paper on malaria in Calcutta in the *Indian Medical Gazette* of March 1906), then a single curve is obtained with two maxima, the first due to the seven-day and the second to malarial fevers. It is not therefore surprising that both these fevers have been so long confused together and regarded as malarial in nature. The late Dr. A. Crombie, I.M.S., may have been thinking of the seven-day fever now described when he stated that, in his belief, 75 per cent of the fevers in Calcutta returned as malaria did not belong to that category.

THE DIFFERENTIAL DIAGNOSIS OF SEVEN-DAY FEVER

From Malaria.—Briefly, the diagnosis of seven-day fever from malaria, with which it has been so long confused, can usually be made clinically by attention to the points described above. The chief of these are, the totally different temperature curve in the cases admitted early, the more severe frontal headache, the red edge to the tongue, the rash when present, the pains all over the body, the absence of enlargement of the spleen and of malarial parasites in the blood, and, especially in the terminal cases, by the slow pulse rate accompanying high fever.

From Influenza.—In Calcutta I find that influenza cases occur mostly from January to March, and disappear in the hot weather before the seven-day fever season commences. They do not appear again till late in the autumn, when the other disease is practically at an end. Further, the temperature curve is usually an irregular, intermittent one, and never shows the typical saddle-back type of the seven-day fever, while the latter is scarcely ever complicated with the inflammatory signs in the lungs and throat which were nearly constant in the Calcutta influenza of 1892.

PAPPATACI FEVER (THREE-DAY FEVER)

One of the results of the much more frequent use of microscopical examinations of the blood in fever cases has been to show that many short fevers formerly looked on as malarial have been found to show no malarial parasites. In 1901 in the Punjab S. R. Christophers and S. P. James found malarial parasites in only 40 to 45 per cent of short fevers, and the latter published some charts and notes of a non-malarial fever of from one to three days' duration. Early in 1906 R. McCarrison described fully a short fever commonly occurring each hot season in Chitral in the extreme north-west of India, one attack of which protected against subsequent exposure to infection. In the same year I examined three years' records of all the fever cases treated in the Lahore Medical College Hospital, and a year's records in a military hospital in the United Provinces, and recognized the frequent occurrence during the hot season months of a similar fever, but found

no cases of the seven-day Calcutta type. Moreover, McCarrison never saw a seven-day chart among over 800 cases in Chitral, while on two occasions the medical officers of regiments from the Punjab stationed in Calcutta have noted that the previous exposure to the Punjab three-day fever gave no immunity against the Calcutta seven-day type. It therefore appears probable that the three-day fever of the Punjab differs from sporadic dengue, in which both three-day and six- and seven-day types have been described.

In 1909, Doerr, Franz and Taussig described fully a three-day fever occurring in the south-east of Europe, which had long been known in Italy, Pick having recorded a clinical description of it as early as 1886, while Taussig in 1905 pointed out its connexion with the bites of a small insect, the *Phlebotomus pappatacii*, which Doerr proved to be the carrier of the infection, and also showed the virus to be present in the blood, but to belong to the group of invisible filterable viruses. Birt working in Malta confirmed many of Doerr's observations.

Distribution.—Pappataci fever is widely prevalent in the countries around the Mediterranean Sea and on its islands, as well as in the south of France and in Portugal and Asia Minor. In Africa, in addition to the northern parts, it has been reported from East Africa, German South-West Africa and South Nigeria, the Sudan, Massawa and South Africa, while the presence of phlebotomi has been reported from South America in Brazil and Peru.

In India this fever is widespread in the Punjab, where Europeans and Gurkhas from the Himalayas are chiefly attacked. Regiments which have been stationed in the Punjab are nearly immune to the disease when sent to such infected places as Chitral, although they suffer in Calcutta from sporadic dengue as already mentioned. The fever is also common in the United Provinces, and has been reported from Dinapore in the extreme west of Bihar, while Hale has reported it from Kamptee in the Central Provinces, but I have not seen it in Calcutta. Several thousand cases occur annually in the army in India. Aden is also infected.

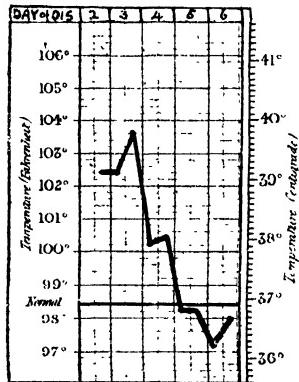
In China, Bolt reports both the fever and sand-flies at Pekin, while a short fever without sand-flies has been recorded in Singapore.

Etiology.—Doerr conclusively proved the virus to be present in the blood during the early stages of the disease, and to be able to pass through the pores of a filter which retained the microcococcus melitensis. He also fed pappataci flies (sand-flies) on the blood of patients with the fever and infected persons living outside the endemic areas, thus proving the disease to be carried by phlebotomi or sand-flies, and Birt confirmed this observation. The incubation period varied between three and seven days. The geographical distribution in various countries has been found to agree very closely with the prevalence of these minute flies. The only animal reported to have been infected artificially was a monkey. As the flies only become infective seven days or more after being fed on a fever case the invisible virus is probably a protozoal organism undergoing a part of its life cycle in the sand-flies. The fever is only prevalent in the summer months, McCarrison stating that a temperature of 75° F. is necessary for its development in Chitral, and that the disease rapidly dies out if infected troops are moved to places at a height with a lower temperature.

Prophylaxis.—Sand-flies are so numerous in endemic areas that prophylaxis is extremely difficult. The flies are very small, measuring not more than 1 mm. in length, so they can pass through an ordinary mosquito net, while Doerr found that any net which has sufficiently fine enough meshes to keep them out allows of insufficient ventilation. The flies bite in the dark chiefly inside houses. Their larvae are very minute, and have been found in the crevices of the damp walls of ruined buildings, which should therefore be destroyed in the neighbourhood of dwellings. Placing pieces of camphor within mosquito nets on going to bed has been recommended for keeping out sand-flies, while iodine applied to the bites is said to remove irritation, while if done quickly may possibly also prevent infection, although this is doubtful. How the infection is carried over the winter, when no cases of the fever occur, is unknown, but it seems most probable that the organism is transmitted through the eggs and larvae to further generations of flies, as in the case of ticks and relapsing fever. Formalin-spraying has been advised for destroying sand-flies. Punkahs and electric fans have also been recommended as a preventative measure. Removing to bedrooms on an upper floor combined with covering neighbouring broken masonry with lime to check the breeding of sand-flies was effective in stopping one epidemic. Evacuation of an infected place may also be effective. Although the disease is a mild one, when widely prevalent it causes the loss of a great many working days. Six varieties of phlebotomi in addition to *P. pappataci* have been described by Annandale in India.

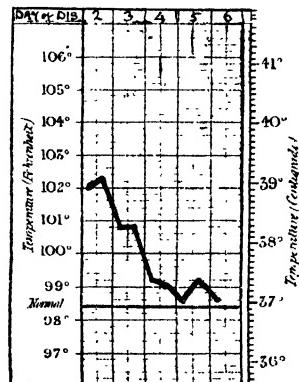
Immunity.—Relapses of an attack have been frequently met with, but lengthy immunity ultimately results, which some believe lasts for life. The blood of recovered patients has been shown by Doerr to render that of infected persons inert when injected, so the serum must have contained some antidote, indicating an active type of immunity.

CHART 69



Three-day fever.

CHART 70

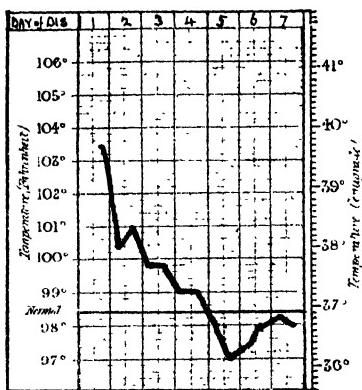


Three-day fever.

resulting from an attack of the fever. This explains how newcomers are attacked so much more than the local inhabitants, most of whom have doubtless suffered previously.

The Temperature Curve.—The patient usually comes to hospital with a temperature of from 102° to 103°, occasionally reaching 104°. It may rise a degree after admission, but more commonly it shows a steady decline of 1° to 2° daily, the morning and evening temperatures being about the same on each day, thus giving a step-like form to the fall, as shown in Charts 69 and 70, or the evening reading may be very slightly higher than the morning, as in Chart 71. A subnormal point is commonly reached and maintained for twenty-four hours or so after the decline at the end of two or three days. The pulse is usually slow throughout, rarely exceeding 100, as shown in Chart 71. This steady step-like decline of the pyrexia is totally unlike that of a malarial fever, and together with the slow pulse should readily allow of the differentiation between the two classes by clinical observation, which will be confirmed by an absence of the malarial parasites from the blood in the three-day form.

CHART 71



Three-day fever.

Symptoms.—According to McCarrison, the fever begins suddenly, sometimes with some previous malaise, but without rigor, although slight chilliness may be present. It is accompanied by severe frontal headache and pain in the eyes from the first, together with pains in the limbs, joints and all over the body. The face was flushed, but no rash appeared, the tongue was furred in the centre, but red at the edges, the bowels usually constipated, sickness rare, and no herpes was noted. The pulse may be rapid at first, but is often only between 80 and 90 with a temperature of from 103° to 104°. The throat was frequently congested, but there was no coryza. Quinine had no effect on the course of the fever, nor did it possess any prophylactic virtue. One attack protects against a second to a great extent. There was no evidence that the disease was contagious, but Europeans and Gurkhas were most susceptible.

The Blood Changes.—McCarrison found the leucocytes decreased during the fall of the fever to 4000 or less, the average in 20 cases having been 5250. In thirty-three differential counts his results averaged the following: polynuclears 61.7, lymphocytes 23.3, large mononuclears 14, and eosinophiles 2.7 per cent. In some slides of Chitral fever cases sent me several years ago by R. P. Wilson, I.M.S., I obtained very similar (hitherto unpublished) results, and noted the increase of the large mononuclears with an absence of malarial parasites; so that in this disease, as well as in seven-day fever and kala-azar, a large mononuclear increase occurs in the absence of malaria. Harnett also found an eosinophile increase during convalescence in three-day fever in India.

Diagnosis.—The characteristic temperature curve; the absence of rigors, recurrent paroxysms of fever, and of malarial parasites in the blood; its incidence in the hot season

being found chiefly among Europeans or newcomers : there are the principal points on which reliance must be placed in the differentiation of this fever.

Treatment.—No drug of specific value in this disease is yet known, but salicylates appear to be indicated for the aching pains.

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XIV. PLAGUE

Recent History and Geographical Distribution.—The modern history of plague commences with the outbreak of the pandemic in 1894, which spread to India and subsequently nearly all over the world. Previous to that date the disease, according to C. J. Martin, was endemic in Siberia, east of Lake Baikal near the Mongolian and Manchurian frontiers, at Solenko in Manchuria, in Yunman in South China, extending from there to the port of Pakoi ; in India in the Garhwal and Kumaon Hills of the Himalaya Mountains extending up to Tibet ; in North-East Persia around the southern coast of the Caspian Sea ; in Mesopotamia in the basin of the Tigris and Euphrates Rivers, in Assyria and in Arabia, bordering on the Red Sea, and in Uganda on the south-west shores of the Nyanza Lake.

The pandemic commenced in China in 1894, affecting Canton and soon after Hongkong that year, and a number of other Chinese ports in 1895. In 1896 it broke out in Formosa, and, more important, in Bombay. In 1898 Jeddah, Madagascar and Mauritius became involved, and in the following year other African ports, and those of the Persian Gulf and the Red Sea, and Alexandria, were attacked, while the disease also spread as far as the Straits Settlements, Japan, Honolulu and New Caledonia, Porto Rico and South America, and by 1900 was prevalent in nearly every quarter of the globe. In 1909 and 1910 a severe epidemic of pneumonic plague broke out in Manchuria, and plague also reached Australia in 1910. By 1913 all the south of Asia from Arabia round to China ; most of the northern and eastern parts of Africa, as well as Senegal and Natal and Cape Colony ; in Europe, Russia, Trieste, Hamburg, and Liverpool and the Tyne, and East Anglia (1910) ; in America several of the larger East Indian islands, Brazil, Ecuador, Peru, Chili and Venezuela, and in Oceania the Philippines, Hawaii Islands and New Caledonia reported cases. In 1914 Ceylon, New Orleans and Catania in Italy suffered, and in 1917 Malta was attacked.

History of Plague in India.—In certain Hindu writings, at least 800 years old, accounts of pestilences, accompanied by death of rats, are to be found, since which time a number of outbreaks believed to have been plague have occurred in India, notably in the seventeenth century on the Bombay side. During the eighteenth century India appears to have been free from the disease, but early in the nineteenth century several recurrences of plague took place of which we have authentic accounts. In 1815 bubonic plague broke out in Kutch and Kathiawar in the north of the Bombay Presidency, following three years of famine, and lasted until 1819, causing much mortality in the crowded and filthy towns. In 1836 a fresh outbreak occurred in the town of Pali in Marwar,

Rajputana, which is generally referred to as "Pali Plague." One-fifth of the inhabitants of this town were carried off, and it spread to a number of villages around. Both pestis minor, and cases which can now be recognized as pneumonic plague, were noted in this outbreak. A sanitary cordon was drawn round the infected area, and the disease died out in two years.

Mahamari.—In addition to the above occasional outbreaks in Western India an endemic focus of the disease has long been known in the Kumaon Hills, which form the southern slope of the Himalayas immediately to the west of Nepaul. Repeated localized outbreaks have taken place here at irregular intervals since 1823, when Mahamari was first discovered. The earlier outbreaks have been well described by McAdam, while a very severe one occurring in 1851–52 was reported on by Francis and Pearson; this presented glandular swellings and was distinctly contagious. In 1853 this outbreak extended to the plains in the Moradabad district, and lingered there until the following year. Since that date a number of smaller outbreaks of Mahamari in the Kumaon Hills, which have been well summarized up to 1894 by G. Hutcheson in the *Transactions* of the first Indian Medical Congress, have occurred. Up to that time the identification of the disease as plague depended on clinical observations, but on the appearance of the disease in an epidemic form in Bombay in 1896 renewed attention was directed to Mahamari, and in 1899 two medical officers were sent by the first Indian Plague Commission to look for the disease in the Kumaon Hills, but they did not meet with any cases. In 1902 a fresh outbreak was reported, in which J. Chaytor White, I.M.S., isolated a bacillus which was recognized by W. H. Hasskine and E. H. Hankin to be identical with the bacillus pestis. It had earlier been suggested by Hankin that the Bombay outbreak may have originated through importation from the Kumaon Hills by some religious mendicants, but it is considered as more likely that it was brought by ship from Hongkong. Further information on the history of plague epidemics can be obtained from W. J. Simpson's treatise on Plague.

The 1896 Outbreak of Plague in India.—The mortality caused by the terrible epidemic of plague which became widespread in Bombay in 1896, and is still prevalent over the greater part of India, is illustrated by Table XXXVI., which shows the annual mortality in each of the British-administered Provinces year by year up to 1905. In 1896–97 the disease was practically limited to the Bombay Presidency, but during the next three years it spread to the other Presidencies, although as yet causing but a comparatively small mortality except in Bengal, which was severely attacked in 1900. In 1901 the total cases rose at a bound from 73,576 to 236,433 on account of a great increase in Bombay and also a marked extension in Bengal and to a less extent in the Punjab. In 1902 the deaths in the Punjab increased by nearly 100,000, while the United Provinces for the first time showed a very severe infection. In 1903 there was a further general increase, with a marked extension to the Central Provinces and the neighbouring Berar, and plague continued to be equally widespread up to 1905, although in the last year there was a great decline in the Bombay Presidency and the Central Provinces, counterbalanced by an equally great increase in the United Provinces. During 1906 the disease also broke out virulently in Burma, and during 1907 a few cases have been

TABLE XXXVI.—YEARLY PROVINCIAL DEATHS FROM PLAGUE IN INDIA

Year.	Total Deaths in British Provinces.	Bombay.	Punjab.	Madras.	Bengal.	Bihar and Orissa.	United Provinces.	Central Provinces and Berar.	Assam.	Burma.
1896	2,219	1,936	a few
1897	48,086	47,710	a few	a few
1898	89,265	86,191	2,019	557	219	..	148	131
1899	102,369	96,596	255	1,658	3,264	..	7	584
1900	73,576	33,196	572	660	38,412	..	135	590
1901	236,433	128,259	16,720	3,035	78,629	..	9,778	9
1902	452,865	184,752	175,645	11,362	32,967	..	48,487	4,647
1903	684,445	281,269	192,068	13,006	65,680	..	80,729	51,514	a few	..
1904	938,010	223,937	396,257	20,125	75,436	..	179,082	42,866
1905	940,821	71,363	334,897	5,788	126,084	..	383,802	12,706	6	..
1906	300,355	51,525	91,712	898	59,619	..	69,660	18,121	74	8637
1907	1,166,223	93,609	608,685	2,872	83,602	..	328,862	37,774	8	9249
1908	113,888	27,345	30,708	3,358	15,948	..	22,878	6,206	..	6752
1909	145,333	24,319	35,655	3,844	11,779	..	38,394	19,216	1	6946
1910	413,355	25,043	135,483	4,867	46,584	..	158,074	28,961	46	7741
1911 ¹	733,582	100,399	175,345	15,185	11,055	73,829	332,301	27,938	27	6060
1912	263,037	28,984	29,805	6,651	1,995	58,324	114,945	19,199	..	3014
1913	198,456	25,288	17,877	5,130	984	36,383	107,683	512	..	4308
1914	266,588	20,060	64,010	5,102	554	64,334	103,954	896	1	7488
1915	380,501	43,824	221,966	3,889	199	27,241	58,128	20,164	..	4640
1916	205,527	79,507	3,278	11,498	110	25,349	49,368	28,619	..	7702

¹ In 1911 Bihar and Orissa, which suffer severely from plague, were separated from Lower Bengal which accounts for the small mortality subsequently recorded in Bengal.

reported west of the Indus. In 1906 there was a general fall of the plague mortality in India to one-third of that of the previous two years, but it was followed by the highest mortality yet recorded in 1907, when the deaths in all India exceeded one million, over half of which occurred in the Punjab alone. Fortunately in 1908 the deaths fell to only one-tenth of that appalling figure, and during the nine years up to 1916 plague has only once carried off over half-a-million people, namely, in 1911. The disease is again unusually prevalent in 1918, so there is no tendency for plague to die out of India, where six and a half million deaths from it have been recorded during twenty-one years. It is noteworthy that the disease has never claimed any great number of victims in the Madras Presidency, which cannot be altogether attributed to the passport system adopted there, while still more striking is the fact that Eastern Bengal and Assam has altogether escaped the epidemic manifestation of plague in spite of imported cases occurring from time to time. In this Eastern Province the want of spreading power of the disease is largely accounted for by the fact that the houses are very rarely closely aggregated into villages, but are nearly all widely separated by rice land one from another, thus naturally limiting the chances of spread by rats burrowing from one hut to another as in the crowded villages of most parts of India.

Seasonal Mortality.—The following information has been derived from an excellent review of the incidence of plague in India published in the Report of the Sanitary Commissioner with the Government of India for 1904. When the epidemic was limited to the Bombay Presidency the greatest prevalence was in September and October, but with the infection of the north of India it shifted to March, and recently has been found in April. There is always a marked fall in the very hot months of May and June, to reach the minimum in June or July, followed by a temporary rise in October, and a steady one beginning from December on.

The remarkably sudden decline of plague with the onset of the hot weather has already been mentioned. This decline takes place earlier in Bihar than in the Punjab in accordance with the hot weather setting in sooner in the former province. Further, the completeness of the disappearance of the disease is in direct ratio with the fierceness of the temperature and the dryness of the air. When the autumn has been unusually hot in Northern India, the onset of plague has been deferred, and the exceptional dryness and heat in the Bombay Presidency in 1900 was accompanied by an extraordinary decline in the plague mortality.

Sex Incidence.—The death-rate is nearly always higher in females than in males, especially in the Punjab and at the time when the disease is most severe. This is explained by their staying at home, and being thus more exposed to infection through rat-fleas.

House Incidence.—The house incidence is most severe in the large closely packed villages of Bihar, the United Provinces, and the Punjab (72 per cent of the people of the Punjab living in large villages), and less so in the scattered homesteads of Lower Bengal and Assam. In large towns, however, two- and three-storied buildings suffer less than single ones, being freer from rats.

Relationship to Rat Infection.—This is very close, for although the infection is usually first carried to a distant place by human beings, or by rats on board ship, yet it is only after these animals become widely infected that the disease becomes indigenous. It commonly spreads to neighbouring houses which are back to back, when there is no direct or easy communication between the inhabitants of them, just as if carried through rat burrows. Dealers in rat-infested grain suffer greatly unless they sleep away from their stores. Those living in stone-paved areas and masonry houses suffer less than the inhabitants of mud-walled houses. The disease is also mostly caught at night in the houses, and by persons going into infected ones after their recent evacuation. Further, a marked reduction in the disease has been observed to follow extensive rat destruction in Bihar, Rangoon and in villages in the Punjab.

The Variations in the Local Conditions in Different Parts of India have also been closely studied by the Second Indian Plague Commission in relationship to the rat-flea theory, with results which confirm its correctness. The two parts of India which have suffered least from plague are Eastern Bengal and Assam in the north-east, and the Madras Presidency, especially its larger eastern portion, in the south. In the case of the former area the country is flooded for several months in the rainy season except for the higher ground occupied by the houses, while the houses are built with much thinner walls than

in most parts of India, and are mostly isolated from each other by water-logged rice-fields; all of which are most unfavourable to the spread of the disease by rats. Moreover, the Commission found the number of rats caught per trap in Eastern Bengal was only one-tenth of that in plague-infested provinces in the north-west of India. The practical immunity of the village population in North-East India is thus readily explained. In the case of Madras the problem was more difficult, as the rats in Madras city were found to be particularly susceptible to plague, while rat-fleas were sufficiently numerous to carry the disease if imported, and the city is the third largest in India, but particularly energetic measures were long in force under the Sanitary Administration. The unloading of ships into small boats lessens the risk of importation of infected rats. Taylor points out that the climate of the Madras Presidency varies greatly in different parts, and the longest period of high flea prevalence occurs in the highest and coolest parts where plague is endemic, and the lowest flea count in the lowest and hottest areas which have escaped plague. Parts nearest to plague-ridden Bombay Presidency also suffered most. In the **United Provinces** Norman White found most plague in the districts which imported most grain and *vice versa*, and considers the carriage of infected rats and fleas in grain second to none in importance in spreading the disease. In another paper with Gloster further evidence was brought forward in favour of this view, while the association of unusual humidity during the winter months with severe plague epidemics was pointed out.

Migration of Rats has often been suspected to play a part in spreading plague, but is difficult to prove. Creel in New Orleans established the fact by trapping marked rats, and found that when set free in a residential quarter 40 out of 160 made widespread excursions, one having travelled a mile in from forty-eight to sixty hours; but when started from near a wholesale provision warehouse only 8 out of 113 made any extensive travel.

The increasing **Immunity** of rats in towns which have suffered much from plague has been established by the Indian Plague Commission, and is least in those which have not suffered from the disease (Madras), and this leads to the hope that in time it may eventually help to cause the disease to die out as the immunity is transmitted by the parents to the offspring.

ETIOLOGY

The appearance of epidemic plague in the large seaports of Canton and Hongkong in 1894 gave bacteriologists the opportunity of discovering the bacillus, which is present in such large numbers in the buboes that it could not be overlooked by modern methods of investigation. Kitasato was the first to demonstrate it at Hongkong in June 1894, while Yersin found it independently very soon after. Numerous European Commissions soon added much to our knowledge of the disease. The Second Indian Commission, working in conjunction with a Committee of the Royal Society and Lister Institute from 1905 to 1914, have worked out very fully the spread of the disease by the rat-flea, a full account of which has been recorded in the supplements to the *Journal of Hygiene* and summarized by C. J. Martin, a member of the Advisory Committee.

Bacteriology.—The plague bacillus is a small bi-polar staining organism growing readily on ordinary media and forming characteristic stalactites in broth with melted butter floating in it, from the under surface of which they grow down into the fluid as long as the flask is undisturbed, and can be well seen by lighting a candle in the incubator behind them. It is present in large numbers in the glands constituting the buboes, from which it can usually be obtained by puncturing with the needle of a syringe especially in the early stages, but commonly disappears if suppuration takes place. In septicaemic cases it can also be easily cultivated from the blood, while the Second Indian Plague Commission have shown that 95 per cent of cases showing more than a very few bacilli in the blood are fatal, so that the organism is present in the circulation at some stage in the great majority of plague cases. In plague pneumonia the bacillus is present in very large numbers in the sputum, while Strong and Teague cultivated it from minute drops of fluid, which are disseminated by such patients on coughing and constitute a grave danger to attendants on these cases, as direct infection may take place in this way. The organism forms toxins, and Rowland has shown that both its virulence and immunizing properties are increased by adding serum or white of egg proteid to the culture media. The **morphology** of the organism is very variable, showing great diversity of form and simulating micrococci, streptococci, streptothrixes and even moulds, as pointed out by the same worker, while when grown in serum containing media it may show a surrounding viscid envelope. The bacillus presents agglutinating properties, but they have not been found to be of much diagnostic value, while Signorelli and Calderola showed that organisms obtained from different parts of the world showed little variation in this property.

The Viability of the plague bacillus outside the body is of importance in connexion with the possibilities of infection. The organism is a delicate one, and rapidly succumbs to the influence of drying and sunlight, and can seldom survive long outside the body in the presence of more hardy saprophytes, although in pure culture it is known to have retained its virulence for over ten years (Wilson). It can survive for months in sterile moist earth, but has never been recovered from the mud floors of naturally infected houses, and only up to four days from grossly artificially infected ones. Hankin found the bacillus died out of grossly contaminated grain in from two to twenty-four hours, while he failed even to infect mice by subcutaneous injections after five days. There is thus no likelihood of grain itself, apart from animal life in it, causing infection.

Animal Infection is of the utmost importance in plague, the intimate simultaneous occurrence of an epizootic in rats and an epidemic in man having been well known at least as early as Moses' time. In addition to rats, natural infection of animals in association with the disease in man has been recorded in the case of the ground squirrel or spermophile in India and America and the tarabagan or marmot, *Arctomys marmota*, of Eastern Siberia, where the infection of this animal is believed to have been intimately related to the terrible outbreak of plague pneumonia in Manchuria in 1909–10. Martin summarizes the evidence of the relationship between rat and human plague in various parts of the world, and concludes that during the fifteen years up to 1911 “no epidemic of bubonic plague has occurred in which preceding or concomitant rat plague has not been discovered on adequate investigation.” **Artificially** rats and mice are readily infected by the injection

of minute doses of plague bacilli, while both rats and monkeys have been also infected by feeding on plague bacilli, but in this case the bubo is always situated in the mesenteric glands, although this never occurred naturally in many thousand infected rats caught and examined in Bombay by the Second Indian Plague Commission's workers, showing that this is not the natural mode of infection of rats. In the Manchurian pneumonic plague outbreak Matsuo recorded the natural infection of donkeys from man. Guinea-pigs are very easily infected by inoculation, and what is of more importance they readily contract the disease when placed in plague-infected houses, and have been used in India for detecting the early infection of habitations and also by Liston for trapping rat-fleas in such houses. Rabbits, cats and ferrets have also been infected, but bovines, pigs and birds are immune.

Insect Infection and the Transmission of Plague.—The intimate relationship between human plague and the epizootic disease in rats, which has been known for centuries, has led to repeated attempts to find the link between the two forms. The important rôle which insects have been proved to play in carrying the infection of other diseases to man, naturally caused attention to be paid to fleas and bugs as possible transmitters of plague on the occurrence of the Bombay epidemic. Numerous observers have found the *B. pestis* in the stomachs of these insects, and especially in the case of the flea. Simond, as early as 1898, produced plague in mice by injecting crushed extracts of fleas from a plague rat, while he did some experiments which indicated that the disease was conveyed from rat to rat only when fleas were present, and suggested that as these insects, while feeding, often discharged the contents of their intestines, which contained plague bacilli, the organisms might become inoculated through the puncture. Ashburton Thompson of Sydney, for epidemiological reasons, persistently supported the rat-flea theory, in spite of Tidswell failing to obtain experimental evidence in its favour. In 1902 Gauthier and Raybaud had some success in obtaining infection of rats through fleas in Marseilles, the *Pulex cheopis* being among those present in that place. In the meantime W. Glen Liston, I.M.S., who had for long been patiently investigating the question in Bombay, in a lecture delivered in 1905 on plague and its relations to rats and fleas, recorded having found that plague bacilli multiplied in the stomach of a flea, since identified by Hon. N. C. Rothschild as *Pulex cheopis*. He also made the remarkable observation that guinea-pigs, naturally infected with plague, harboured numerous rat-fleas, some dead rats having also been found near by. Conceiving the brilliant idea of using guinea-pigs to trap rat-fleas in plague-infected houses, he was able to prove that after rats had died of the disease in a house their fleas could be found on guinea-pigs which had been let loose there, but not on those placed in uninfected rooms. Further, these rat-fleas frequently contained virulent plague bacilli, and the guinea-pigs sometimes contracted plague. He further proved that rat-fleas could be found in considerable numbers on human beings living in houses where rats had died of plague, although they were very rarely found free under ordinary conditions, while the men harbouring them sometimes contracted plague in these houses. Thus he proved that the rat-fleas deserted the dead bodies of their hosts and then attacked human beings.

In 1905 a new Plague Committee was formed by the Secretary of State for India in

conjunction with the Royal Society and the Lister Institute under C. J. Martin, in connexion with which the **Second Indian Plague Commission**, including Liston, Lamb and others, worked in Bombay and other parts of India. The Committee published a series of very detailed reports in the supplements to the *Journal of Hygiene* up to 1915, when the war stopped its work. The results entirely confirmed and greatly extended Liston's work, and the following account is mainly based on them.

Small rooms were constructed in which animals could be exposed to infection in various ways, and it was found that plague could be transmitted from animal to animal only if fleas were present and had access to them. All animals protected from the fleas by a fine meshed wire, or by a surrounding area of a sticky fly-paper, escaped, although controls not so protected commonly took the disease. If fleas were absent, no amount of exposure to contamination with the urine and faeces of infected animals conveyed the disease, although both urine and faeces may contain the plague bacillus. The organisms multiply in the stomachs of the fleas, especially during the height of the plague season, when infection was conveyed up to fifteen days after being fed on a plague animal, but only as long as seven days in the minimum plague months. Cat-fleas did not infect, and human ones only three times in thirty-seven experiments. The bubo in flea-carried plague in guinea-pigs is nearly always cervical.

Experiments were also carried out in plague-infected houses with the following results. Guinea-pigs placed in plague houses attracted many fleas, mostly rat ones, and 29 per cent of these guinea-pigs died of plague, while previous disinfection of the houses did not prevent this transmission. Further, fleas from plague-infected rats found in houses either dead or dying transmitted the disease to healthy animals.

Feeding experiments showed that plague can be transmitted in this way through a number of rats without losing its virulence, while the buboes in that case are mesenteric, indicating infection through the intestinal canal. Many thousand naturally infected rats, however, were dissected, and never showed mesenteric buboes, showing that this is not the ordinary mode of infection in them, in which case again the infection is doubtless carried by fleas. A chronic form of rat plague was met with frequently in the Punjab only, in which abscesses containing the *B. pestis* were found. Its exact epidemiological significance is unknown.

Insect Infection.—As pointed out by the Second Indian Plague Commission, Verjbitski in 1902 showed that bugs, *Cimex lenticularis*, and fleas fed on animals infected with virulent plague bacilli could communicate the disease to healthy animals for three to five days after infection, and he also pointed out the contaminative method of infection through the insects, plague bacillus containing faeces being rubbed into the wound inflicted by their bites. The Second Indian Plague Commission independently made the same observations in ignorance of the Russian observer's work, which had not been published in any scientific journal. They found plague bacilli to multiply greatly in the stomach and intestines down to the rectum of *P. cheopis*, the common rat-flea of tropical and subtropical countries. Both that flea and the usual rat-flea of colder climates, *Ceratophyllus fasciatus*, have been proved to bite man readily when hungry, and during the act faeces containing plague bacilli are extruded from the rectum and can infect the minute wound

caused by the insect's bite. The salivary glands and body cavities of fleas are not invaded by the bacilli, while mechanical conditions prevent regurgitation of fluid from the stomach to the mouth parts in fleas, so direct infection through their bites was probably only of rare occurrence. In 1914 Bacota and Martin recorded a most interesting observation, which threw new light on the question, namely, that in a certain proportion of infected fleas the development of the bacilli is so extensive as to close the alimentary canal at the entrance to the stomach, choking the proventriculus and extending into the oesophagus. Such fleas can still suck blood, but only distend the contaminated oesophagus, some of the infected blood being forced back into the wound on cessation of the pumping action. As such fleas are persistent in their efforts to feed they are particularly dangerous, while they may live for some days, but, being incapable of imbibing fresh fluid, they are in danger of drying up if the air temperature is high and the saturation of the atmosphere low. This may be a factor in explaining the sudden cessation of epidemics in Northern and Central India with the onset of the hot dry season. Kato also independently came to the conclusion that rat-fleas may carry plague infection by their bites. All the evidence goes to incriminate the rat-flea as the main insect carrier of plague, although bugs may occasionally be responsible. De Raadt has also infected rodents through the bites of head lice, *Pediculus capititis*, taken from the hair of a plague patient, while Swellengrebel and Otten had previously found that body lice, *Pediculus hominis*, obtained from the clothing of plague patients could carry the infection of plague, so these insects may play a minor rôle in spreading plague. We may now consider the question of the transmission of plague in the light of the foregoing facts.

We may therefore conclude that although the very rare primary pneumonic type of plague is very infectious to sick attendants or others in the house, yet the common bubonic and septicaemic forms are not at all directly infectious, well-kept plague hospitals in fact having been found to be the safest places during an epidemic because they are free from rat-fleas. Moreover, from 70 to 80 per cent of plague cases in different places occur as single infections in a house, while if more than one occurs they are due to simultaneous infection as a rule, and further attacks among the household rarely take place even when the patient is treated throughout at home. No amount of excreta or soiled clothes from plague-infected animals or men will produce plague in the most susceptible animals in the absence of fleas or, according to Verjbitski, of bugs. On the other hand the most thorough disinfection with strong perchloride of mercury solution of a room in which a plague person has died will not prevent the subsequent infection of guinea-pigs set free there, because this agent, although very powerful against the plague bacillus, does not kill the rat-flea, which can be caught in undiminished numbers after its use. Soil and air infection having been excluded as a common method of infection, while fleas, and especially the rat-flea in India, have been shown to be able readily to convey the infection in the absence of other possible agencies, this insect must now be regarded as the ordinary carrier of the disease from rat to rat and from rat to man. The importance of this fact cannot be overestimated, as all available men and funds can now be concentrated in fighting a known foe by scientifically based methods, instead of dissipating much energy in a large variety of measures of more or less doubtful efficacy.

**THE EPIDEMIOLOGY OF PLAGUE IN THE LIGHT OF THE RAT-FLEA
THEORY OF INFECTION**

So many theories regarding plague have been disproved by the hard logic of steadily accumulating facts concerning the behaviour of the disease under diverse conditions and in diverse places, that it will be well to review briefly the main facts of its epidemiology, in order to see how far they comply with the demands of the rat-flea theory of infection ; for unless it will stand this test it is not likely to exert due weight in ensuring the adoption of practical measures for combating this terrible scourge of humanity.

Plague is primarily an Epizootic in Rats.—Although isolated cases of plague may occur in a town or village as a result of importation of the disease by human agency, yet the disease does not become epidemic among the population until rats have begun to die in unusual numbers from plague, that is until plague has become epizootic among the rats. Ashburton Thompson carefully studied this relationship in Sydney, where repeated small outbreaks have occurred since 1900. He systematically examined rats from the infected quarters and demonstrated that the epizootic area was practically co-extensive with the epidemic area. Hunter made similar extensive observations in Hongkong and found the curves of infection in rats and man ran a closely parallel course, only both the rise and the fall of the rat disease was about a fortnight before that of the human cases. Moreover, after the decline of the epidemic the number of infected rats also remained low. Kitasato and others found the same time relationship of the disease in rats and men in Japan. More recently the Bombay Plague Commission have fully established this relationship by very extensive investigations, and found the mean interval between the epizootic in *Mus rattus* to be approximately ten to fourteen days, varying from three and a half weeks at the beginning of the rise, through two weeks at its height, to only a week during the second well-marked apex. This interval they explain by allowing three days before the rat-flea bites man, three days for the incubation period in man, and five and a half days for the average duration of the illness in fatal human plague.

Relationship of the Spread of the Disease in Villages to Rat Infection.—Striking confirmation of the spread of plague by means of rats is afforded by the distribution of the disease in Indian villages. Those of the areas which have suffered most severely from plague are built of mud walls, usually back to back, but frequently, in order to pass from one house to another against which it abuts, it is necessary to traverse a quarter of a mile or so of narrow lanes. Moreover, owing to differences in caste it is common for the inhabitants of one house never to hold any intercourse with those of contiguous ones. Under these conditions it is found that the disease does not spread from one household to another of the same caste with whom they have social intercourse, but the reverse is usually the case. In the earlier days of the present pandemic, a common preventative measure was to unroof the houses in which plague cases had occurred, in order to utilize the powerful disinfecting rays of the sun, and to prevent the owners from prematurely reoccupying them. It was then frequently observed that the unroofed houses formed a continuous series, although quite irrespective of the facilities for human intercourse between one another. Now these mud-walled houses are infested with *Mus rattus*, the common house

rat of Indian villages, and their burrows in the floors and walls form a continuous connexion down the rows of infected huts, so that the distribution of the disease is at once most simply explained by the knowledge that plague is communicable from rat to rat and from rat to man.

A remarkable piece of evidence connecting the epizootic among rats with the infectiveness of the houses is furnished by the observations of the Bombay Plague Commission in the village of Sion Koliwada, which was under their close observation both before and after the infection of the place. In the antecedent period no plague had been found among trapped rats. Then human plague appeared after the death of a rat which had been concealed, and the villagers evacuated the village almost completely. The Commission at once proceeded to watch the epizootic among the rats which had now begun and also to test the infectivity of the houses by means of placing susceptible guinea-pigs in each hut in cages, some of which were so constructed that the animals could not come into contact with the soil, although they were within the reach of fleas. Although, so far as could be ascertained, only one case of human plague had been introduced into the village, the disease spread steadily through the rats for two months, and no less than 45 per cent of the buildings were eventually proved to be infective to the guinea-pigs, although direct spread from one animal to another was excluded, and the conditions were such that the only mode of transference of the disease was by means of the rat-fleas, which were caught in abundance on the animals and some of which were proved to contain the plague bacillus. By these means a clear picture of the spread of the disease from rat to rat and from rat to guinea-pig was obtained, such as is not possible in the case of human plague.

Species of Rats and Plague.—The commonest species of rat in India is the domestic *Mus rattus*, which appears to be the only species associated with plague met with in all parts of India yet examined, except in the great seaports. As it lives in the houses and is tolerated there by the people, it has ample opportunities for spreading plague. The rats of the large ports present curious differences in various parts of India. Thus, Dr. Hossack, who first carefully studied the question in India from the zoological point of view, found that *Mus rattus* was comparatively rare in Calcutta, *Mus decumanus* was common, but the preponderating rodent was the common field rat, *Nesokia Bengalensis*, all of these being susceptible to plague. In Bombay the Plague Commission found 70 per cent of the total and 84·6 per cent of the infected rats were *Mus decumanus*, the great majority of the remainder being *Mus rattus*. *Mus decumanus* lives mainly in gulleys and drains, but is also found in burrows in stables, and is not infrequently trapped in Bombay houses, even above the ground floor, usually climbing up pipes. This is now the common rat of Europe and of ships, through which it has probably reached tropical ports. According to the Bombay workers the plague epizootic begins each year in *M. decumanus* some ten days earlier than in *M. rattus*, the latter being infected after the former, which is the primary cause of the outbreak. Captain Lloyd, I.M.S., has recently examined large numbers of rats from various parts of India, and finds that *Mus decumanus* is not common in Rangoon, while it appears to be absent from Madras city, as he found none among over 1000 examined : a point of great interest in connexion with the very slight amount of plague which has occurred in Madras town. He also observes that the rats of

particular towns commonly have such a close family likeness that the place of origin can with experience be at once detected.

Mus ratus can be distinguished by the fact that its long-ringed dark-coloured tail is longer than its head and body put together. Its ears are large and thin, while its colour varies widely from a light brown to black, the belly being always of a lighter shade. *Mus decumanus*, on the other hand, has a tail shorter than the head and body together. The ears are smaller than in *Mus ratus* and the nose almost Roman, while the colour is brownish grey and less variable than in the former species.

The Seasonal Incidence of Plague.—Plague presents a peculiarly well-marked seasonal incidence, with a very rapid rise to the maximum within a few weeks and a nearly equally rapid decline. Nevertheless, it reaches its maximum at very different periods of the year in different places, in a remarkable manner, and at the same time recurs at the same season year after year in any given place. Thus, in Bombay the season of plague is from January to April, and in Calcutta from February to May. Yet in Poona, at a distance of only eighty miles from Bombay, but at about 2000 feet above sea-level, with the exception of a slight outbreak during February and March in the year it was introduced, the regular annual season is between August and the following March, the maximum being somewhat variable. In the Punjab the marked seasonal increase occurs from March to May, while in the hot months from June to September it is never epidemic, but there is a tendency to rerudescence during the winter months, leading up to the annual great outbreak. Thus the late cold weather and early hot season is the regular plague season in India, and there is a marked decrease as soon as the mean temperature rises to 85° F. The Bombay Commission associate this with their observation that the plague bacillus flourishes less well in the rat-flea at this high temperature, and infection is less readily experimentally transmitted. They also find much less plague among rats in the quiescent season, during which time breeding among them is more rapid than at other periods, and thus a large number of young and susceptible rodents accumulate among which the epizootic can rapidly spread at the beginning of the next plague season. Moreover, they found more fleas in the plague season and less in the months when plague was at its minimum both in Bombay and in the Punjab.

The seasonal variations of plague can thus be readily explained in relation to the annually recurring epizootic among the rats, which ceases as a result of the death of a great many and acquired immunity of others, leaving but few susceptible at the end of the rat outbreak. Yet, owing to their enormous capacity for breeding, these pests once more afford suitable conditions for the recurrence of the disease at the most favourable period of the following year.

The Spread of Plague from Place to Place.—It has been frequently suggested that plague may be carried from village to village by the migration of rats, but in the absence of reliable evidence of such an occurrence this is highly improbable, at any rate as an important method of extension of the disease. Rats may doubtless be carried by ship from one country to another and if the plague is prevalent among them some of the infected animals might escape from the vessel and infect the port of arrival, and measures are certainly necessary to prevent the possibility of such a calamity. Even in this case

the disease is probably more frequently carried by the human host, or according to the Plague Commission by infected rat-fleas carried by man. In the case of spread by land the disease is certainly mainly conveyed from place to place by persons infected going to uninfected areas during the incubation or early invasion stages. Frequently there is no immediate spread of the disease, especially if it is the season of decline of the epidemic, but subsequently rats begin to die of plague and an epidemic breaks out in the town or village.

Recrudescence of Plague.—In large towns, such as Calcutta and Bombay, the intervals between the annual epidemics are bridged over by continued infection of rats and to a much less extent of human beings. In small towns and villages, however, there is commonly no evidence of the continuation of the disease in either rodents or man for many months, yet there is a marked tendency for plague to recur in the same places year after year. The very important practical question arises whether in the quiescent period plague only remains in the few towns where occasional cases continue throughout the year, and the next epidemic is due to re-importation from these few centres into numerous places from which the disease had completely died out; or whether it really remains latent in a large number of places and recrudesces in them during the favourable season of the year. If the latter is the case the prevention of the yearly outbreaks is an infinitely more difficult procedure than if the disease persists in only a few places, where drastic measures for stamping it out in the long quiescent period would be advisable. This question has been most carefully studied in the Punjab by S. Browning-Smith, I.M.S., who has had over six years' experience of plague work, while in 1907-8 a very special effort was made by him to obtain evidence on this important point. His results may be briefly summarized in the following table from his paper read before the Bombay Medical Congress.

TABLE XXXVII.—MODE OF RECURRENCE OF PLAGUE IN PUNJAB VILLAGES

	Cases.	Percentage.
1. No interval	11	4·0
2. Importation by human cases	52	18·8
3. Importation by clothes, etc.	18	6·5
4. Importation possible but indefinite	70	25·2
5. Recrudescence	126	45·5

Many of the cases classed under 4 were probably examples of recrudescence, but owing to plague being present in neighbouring villages it was impossible to exclude absolutely importation, so that well over 50 per cent of the outbreaks were certainly due to recrudescence. The Bombay Commission investigated the conditions in two Punjab villages, but found no rats dying of plague for considerable periods, yet the disease recrudesced in one of them without their being able to trace any evidence of importation. They met with a few instances of chronic abscesses containing plague bacilli in rats, which may possibly be a factor in carrying on the infection over the long quiescent period. The heat in the Punjab is very great during the period of decline and quiescence of the disease,

and certainly is an important factor in causing the temporary disappearance of the disease. Recrudescence, then, is a very important and serious fact in connexion with the epidemiology of plague in the innumerable small towns and villages of the infected areas of India, although the usual manner of its recurrence is still very imperfectly understood.

PROPHYLAXIS

The establishment of the rat-flea mode of infection of plague allows of greater precision in carrying out prophylactic measures against the disease, and saves much waste of energy and funds over comparatively useless measures, especially as regards disinfection of houses by methods which leave rats and their fleas untouched. As an outbreak of plague is always preceded or accompanied by an epizootic in rats, measures directed against these animals are of the first importance, as it is said that if the number of rats can be reduced by 65 per cent human plague cannot continue.

The Destruction of Rats.—An immense amount of work has been done in plague-infected places to ascertain the best method of destroying rats in sufficient numbers to reduce materially these very prolific animals, but opinions still differ on the subject, while local conditions will necessarily affect the problem. The following are the more generally used plans. **Trapping** rats has been widely resorted to, especially in India, where wire cages are chiefly used. They must be thoroughly washed and cleaned daily or rats will avoid them. The number employed must not be less than 2 per cent of the population, while in the Punjab even that number failed to reduce the rat population in villages, and this method was found impracticable on a large scale. Heiser states that spring traps are ten times as effective as wire cages, and the latter better than poisoning. Trapping has also been recommended as the best measure on ships. **Poisoning** of rats has been much used with varying success. Kitano in Japan found phosphorus the most effective and arsenic next, either being intimately mixed with grain or other food, and in Yokohama 280,000 rats were thus destroyed in 1913, but only 130,000 in 1914, showing a great reduction. In the Punjab, however, poisoning of rats was not a success. In Madras, King employed sulphuric acid mixed with crude gas tar for placing in rat holes and around food, etc., to be protected from rats. In Constantine, Billet "chlorinated" sewers by first pouring in a one-third solution of chloride of lime and half-an-hour after a one-third solution of hydrochloric acid, which set free chlorine gas. Two live electric wires with a bait suspended between them over water have also been used to deal with rats. **Fumigation** with various gases is of great value in the case of houses, grain stores and ships. Sulphur dioxide has been most used, but to be certain to destroy rats and their fleas the gas should be present in a strength of 4 to 6 per cent for some four hours, although some workers have claimed success with lower strengths. In the United States 5 lb. of sulphur per 1000 cubic feet for seven hours for living quarters, giving a 4 to 6 per cent strength, and for holds of ships a 3 per cent strength acting for twelve hours, are used. The Clayton apparatus has been of much service in fumigating ships. Hydrocyanic acid gas is also very effective especially for grain stores, barges, etc., infested with rats and their fleas, and has been used by Liston in Bombay and Guiteras in Havana.

Liston found that half an ounce of potassium cyanide per 100 cubic feet sufficed to disinfect a barge of 12,000 feet capacity, nearly all the rats and fleas being killed in four hours, although many survived one hour.

Rat-Proofing of houses, food stores and even docks has been largely resorted to as a protection against rats carrying the infection of plague, and has the advantage of being a permanent measure not requiring continuous repetition as in the case of rat destruction, so that it is cheaper in the long run. In Shanghai, Driel used for this purpose tar macadam placed under the wooden floors. Concrete has, however, been more generally employed, and should be at least 3 inches in thickness, while brick walls not less than 6 inches in thickness should extend at least 18 inches down into the soil. Sewers should have smooth vertical walls 3 feet high, as rats cannot jump more than about 2 feet. These measures have been used in India, America, the West Indies, Java, Japan and other places, and reported favourably on as an important anti-plague measure.

Evacuation of Houses has been very largely resorted to in India, especially in the Punjab and Central Provinces, where the plague season mainly occurs in the dry cold and early hot weather with practically no rain for five or six months. The people now readily resort to this simple and economical method of escaping from the dangerous infected rats, and recognize the occurrence of a number of dead rats as a danger signal. When plague becomes prevalent in Nagpur both Europeans and well-to-do educated Indians make use of the susceptibility of guinea-pigs to keep them in cages in their houses, and if they die at once evacuate the residence, an excellent precautionary measure. In the Punjab, where the campaign against rats has not proved a success, evacuation of villages at the first appearance of the disease is now looked on as the best measure to adopt. Evacuation of infected houses immediately on the first occurrence of plague in a town, if the disease is detected sufficiently early, has also proved of great value in stamping out the disease before it has become widespread, but very energetic and complete measures are necessary to ensure success. Thus Guiteras reports an outbreak of the disease at Havana with 3 cases, in which seventeen blocks of houses were completely depopulated within twenty-four hours. They were then disinfected, and made rat-proof, and the people allowed to return after three weeks, this radical measure having proved successful in stopping the outbreak. It is of interest to note that during outbreaks of Mahamari, or plague, in the Kumaon Himalayas the uneducated people for generations have followed the custom of deserting their villages on the occurrence of any unusual mortality among the rats, even before they were themselves attacked by plague, and do not return to their houses for weeks or even months.

Inoculation.—It is seldom that the foregoing measures can be carried out, especially in the East, sufficiently early and completely to do more than mitigate outbreaks of plague, so personal protection against the disease during an outbreak is of the greatest possible value. This is undoubtedly afforded by inoculation with Haskine's vaccine, which has been greatly improved, especially as regards the reduction in the severity of the attending reaction, by later modifications. The most conclusive evidence of its protective power is the fact that so many workers have been able to continue their investigations year

after year without accidental infection in the Bombay Plague Laboratory, handling and examining infected rats and rat-fleas under circumstances which made it impossible to avoid their being repeatedly bitten by infected fleas. One observer recommends such laboratory workers to be inoculated every six months. It will suffice to quote only a few figures. Bannerman reported that the immunity lasted for from six months to a year or more, and that among a large number of municipal employees, all equally exposed to infection, the incidence was 0·19, and the mortality 0·18 among the inoculated, against 6·7 and 6·2 respectively in the unprotected. Liston gives the following selected figures for 1911 in thirty tables which are summarized as follows in the *Tropical Diseases Bulletin*.

TABLE XXXVIII.

Population.	Attacks.	Deaths.	Cases per 1000.	Case mortality.
Inoculated 118,148	941	371	7·96	39·5
Uninoculated 321,621	11,041	8695	34·4	78·6

These figures are sufficiently extensive and striking to speak for themselves. In Bangalore success was obtained by Standage by a house-to-house campaign. Dunn found evidence that the protection lasts in villages as long as two years. Protection seems to result very quickly, and the negative phase is very short or absent according to Bannerman, while Stevenson found experimentally in rats that it is absent, and protection commences to be evident in a few hours, and goes on increasing for two or three days. Anti-plague vaccine can therefore be safely used in infected houses. Liston found that storage mitigates the severity of the reaction without lessening the protective power, and advises the use of a vaccine made from a two months' growth and stored for some months not exceeding eighteen. After four years vaccines had lost all their protective power. Devy also advises vaccines four to six months old as the best. Rowland has done valuable work in testing the best methods of culture for preparing active vaccines with high immunizing powers, and recommends the addition of serum to the media. He found sensitized vaccines of little value, and also failed to produce good immunity with the attenuated living cultures, which were advised and used in the Philippines by Strong. He got most immunity by the use of a nucleo-protein extracted from serum-grown virulent strains of plague bacilli, but the Bombay workers failed to get good results in plague cases with a horse serum prepared with the aid of nucleo-proteins.

CLINICAL DESCRIPTION OF PLAGUE

Plague is perhaps the most variable of all specific infectious diseases, so that, while nothing is easier than to diagnose a group of typical bubonic cases, yet few more difficult problems are met with than the differentiation of anomalous examples of the affection, such as present themselves in the form of pestis minor, a very mild form of the bubonic disease, or the pneumonic and septicaemic forms. As the great majority of the cases present the bubonic form this will first be described, and the variations met with in the other typical varieties will be subsequently pointed out.

TYPICAL BUBONIC PLAGUE

History of Onset.—Many of the severer cases of bubonic plague are quite unable to give any account of themselves when they first come under observation, but in such the clinical picture is commonly too clear to permit of any difficulty of diagnosis arising. When the history of the onset of the disease can be obtained from either the patient or his friends it is usually found that it was quite sudden. In some, however, **premonitory** symptoms may have preceded the actual onset from a few hours to one or two days, such as lassitude, giddiness, frontal headache, furred tongue, sickness and diarrhoea, and mental dulness, pains in the limbs and sometimes also over the sites of subsequent buboes. The actual invasion of the disease is sudden, commonly with rigors or chilliness, sickness, severe frontal headache, congested conjunctiva producing redness of the eyes, giddiness and sometimes unsteady gait as if intoxicated. Aching pains in the back and limbs and sometimes in the abdomen may also occur. The temperature rises rapidly to a high degree, and the fever is accompanied by very severe constitutional disturbance, with marked bodily prostration, early mental hebetude, and dull appearance, while the speech becomes slow and the utterance thick. As the disease progresses, either great restlessness, or drowsiness and delirium, sometimes of a violent nature, supervene, gradually deepening into a pronounced typhoid state accompanied by muscular twitchings. Sometimes the mental condition remains clear throughout, or consciousness may return for a time shortly before death.

The Tongue shows a thick coating of fur on the dorsum, becoming brown and dry in the later stages, while the tip and edges remain red and papillae may also be seen through the fur.

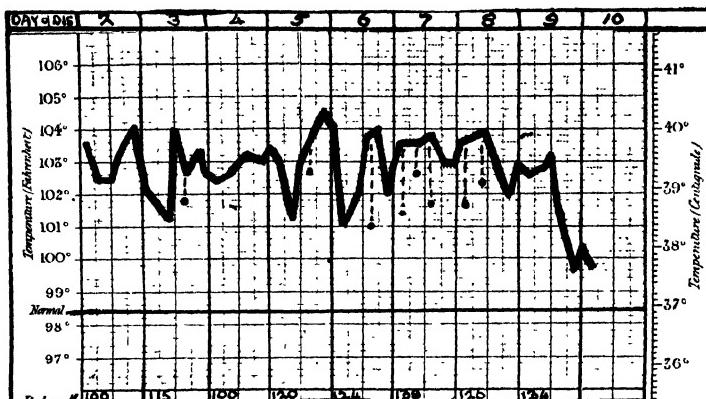
The Pulse is rapid throughout, averaging about 120 a minute, but reaching a much higher rate in the later stages. It is soft and often dirotic, and in fatal cases may ultimately show a tendency occasionally to drop a beat, thus foreshadowing the frequent sudden terminal cardiac failure, which may even take place after convalescence appears to be well established. The respirations are also markedly accelerated, reaching from 30 to 40 a minute.

The Spleen is early enlarged to a moderate degree, projecting slightly below the costal margin as a rule, while the **liver** is commonly also slightly increased in size, and the abdomen may occasionally become distended.

Buboes are, however, the most characteristic and important feature of the common form of plague. The first indication of them is usually pain, often intense, over the site of a group of lymphatic glands accompanied by marked tenderness. This is quickly followed by slight enlargement of the glands themselves, with much inflammatory oedematous swelling around them, producing anything from a small hard tense swelling to a large boggy mass the size of an orange, which may take from a few hours to several days to develop. They are commonly accompanied by great pain, causing the patient to flex the thigh or to extend the arm at right angles to the body, in accordance with the position of the bubo in the groin or axilla. In about two-thirds of the cases the bubo is situated

in the groin, in from 15 to 20 per cent in the axilla, in about 10 per cent in the sub-maxillary or cervical region, while in rare cases it may occur in the popliteal space or in the supratrochlear gland just above the inner side of the elbow, and occasionally more than one

CHART 72

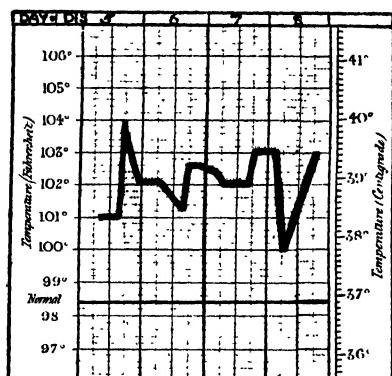


Severe fatal bubonic plague in a European.

group of glands may be affected one after the other. In the majority of patients who live long enough the buboes suppurate during the second week, and ultimate healing takes place slowly as a rule, the process sometimes taking many weeks, during which death from marasmus may occur. In mild cases slow resolution may take place without breaking down, induration of the glands sometimes persisting for a long period.

The Temperature Curve.—The type of fever in plague is somewhat variable. The temperature rises rapidly and reaches its height in one or two days. In severe cases it presents the high continued type from 102° to 104° or more, but with a tendency to irregular remissions of several degrees in extent, occurring especially in the later stages on from the third to the fifth day, and commonly followed by a marked rise shortly before death, as shown in Chart 73. In more favourable cases the curve is more remittent in character, as in Chart 75, falling to normal by lysis between the fifth and seventh days when recovery takes place, but showing a slighter degree of remittent or intermittent fever during the stage of suppuration of the bubo, as shown in Chart 74. A severe and prolonged case in a European with a cervical bubo is shown

CHART 73

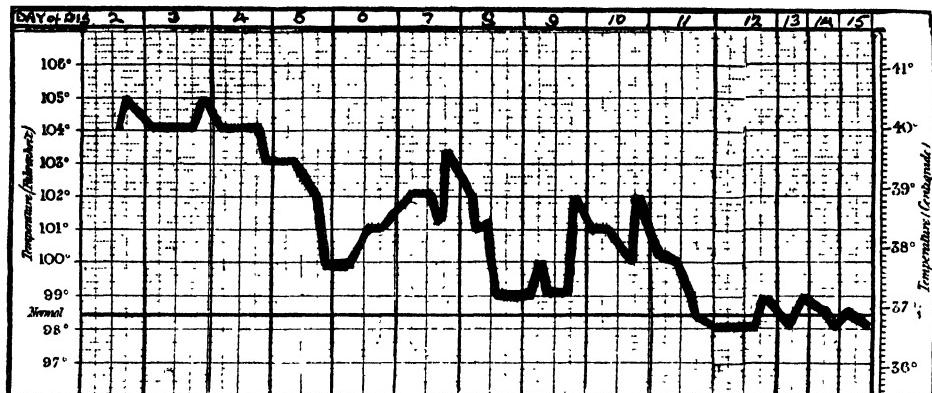


Bubonic plague, showing temporary remission shortly before death.

in Chart 72, which illustrates the greater resisting power of Europeans, and also the rapid pulse throughout the disease.

Duration of the Disease.—In Calcutta half the cases admitted died within two days,

CHART 74

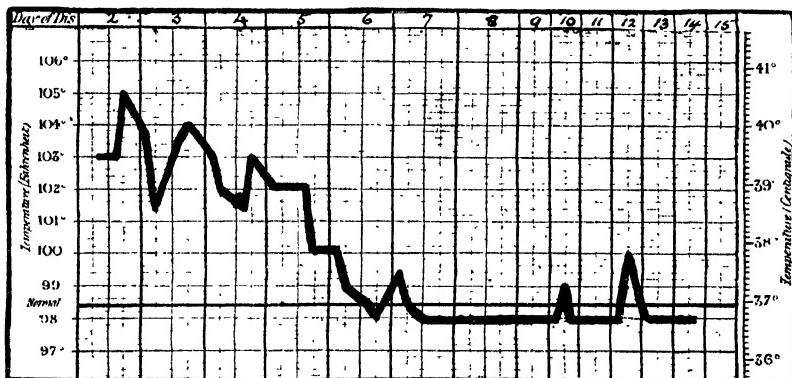


Bubonic plague with suppuration of bubo, and recovery.

and in another third the fever lasted only three or four days after admission. The history of illness before admission averaged just under four days. Convalescence is very slow.

Primary Vesicles and Pustules.—In a small proportion of bubonic plague cases a

CHART 75



Bubonic plague, with recovery. B. pestis obtained in pure culture from the primary vesicle.

primary lesion, in the form of a vesicle or pustule, can be found on the skin area which is drained by the affected lymphatic glands, consequently on the lower extremities in the majority of cases. These lesions are most important owing to their occurring especially

in the mildest and least characteristic cases, while, as they contain a pure culture of the plague bacillus, they furnish a ready means of confirming the diagnosis by the microscopical and cultivation tests. The writer has obtained pure cultures from such lesions in a number of plague cases in the Medical College Hospital, Calcutta, and Charts 74 and 75 are both from cases in which the diagnosis was confirmed in this way by J. W. I. Megaw, I.M.S.

R. Knowles has recorded the case of a girl of eight years in whom the primary bubo was found post mortem in the mesenteric glands and the caccum and small intestine showed numerous ulcers. Montel saw five cases of plague in Saigon with cervical buboes and diphtheritic lesions on the tonsils, which he regarded as the primary lesions.

Carbuncles have only occasionally been met with in the present Indian plague epidemic, but I have seen one such case in which the lesion was situated on the breast of a native woman, the lesion, together with the axillary glands, being removed in the surgical wards under the impression that the disease was malignant pustule, but mixed plague bacilli and streptococci were cultivated from the breast lesion, and pure plague bacilli from the glands; the case ultimately proved fatal, well illustrating the great difficulty in the diagnosis of some cases of plague.

PESTIS MINOR

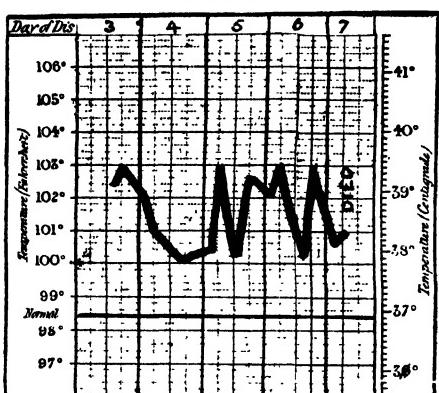
During outbreaks of plague very mild ambulant cases are occasionally met with, which may present great difficulties in diagnosis, and hence are liable to be overlooked. They show only a slight degree of fever, with some tenderness and enlargement of a group of glands, but without the severe constitutional disturbance of typical bubonic plague, while they may continue to move about and only lie up for a short time, if at all. Such cases are exceedingly difficult to differentiate from slight septic infections and the so-called climatic buboes, unless they happen to occur in plague-infected houses, or among coolies employed in plague-disinfection work, among whom this form of the disease is not very rarely seen. In doubtful cases a bacteriological examination of fluid obtained from the affected glands by means of a hypodermic syringe will alone clear up the case. In some instances a number of such cases occurring in the absence of any typical plague have been described as pestis minor, but in the absence of bacteriological confirmation it seems more probable that they were only " climatic buboes " as Sheube suggests.

SEPTICAEMIC PLAGUE

At the opposite end of the scale to pestis minor we have a fulminant type of plague—the pestis siderans of old writers—in which the organism of the disease invades the blood stream without first producing the characteristic local infection of a group of lymphatic glands, which constitutes the essential feature of the bubonic form. It causes a rapidly fatal septicaemia. Philip and Hirst record numerous septicaemic cases in the 1914-15 outbreak of plague in Ceylon. Attention was first attracted by a series of sudden deaths in a crowded insanitary quarter near the harbour, and investigation showed that within two weeks 18 out of 19 such cases were septicaemic plague, while the accompanying disease in rats was also proved to be mainly septicaemic. There was a remarkable absence

of distinctive post-mortem signs both in man and in rats, cultures being necessary to establish the diagnosis. Out of 412 cases no less than 246 were septicaemic, with a mortality of 100 per cent. Of the two species of rats most frequently infected, *Epimys rufuscens* and *Epimys norvegicus*, the former showed twice as high a percentage of septicaemic cases as the latter. This form may present great difficulties of diagnosis, especially when seen early in an outbreak of plague, but the severe constitutional symptoms of sudden onset, with congested suffused eyes, very rapid soft pulse, some tenderness of all the superficial lymphatic glands without definite enlargement, swollen and tender spleen, delirium and fever of a high degree from the very first, with a tendency to early

CHART 76



collapse constitute a clinical picture which will generally allow of a correct diagnosis being made, which may be confirmed, if necessary, in the later stages of the disease by finding the bacillus in the blood by microscopical or cultural tests. In some cases the temperature may be of a low remittent type, scarcely rising above 100° F. owing to feeble reaction of the system to an overwhelming dose of toxins, while the curve tends to be more remittent than in the other forms of plague, as shown in Chart 76. The disease may be fatal within twenty-four hours, and usually terminates in two or three days, but in rare cases which survive longer a bubo may appear in the later stages of the disease. Lafont, Lecomte and Heckenroth report from

West Africa a case of apparently primary cerebro-spinal meningitis due to the plague bacillus verified by culture and animal inoculation.

PNEUMONIC PLAGUE

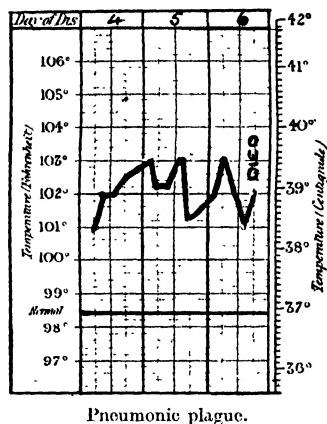
In the Bombay outbreak L. F. Childe, I.M.S., noticed the occurrence of a number of rapidly fatal cases of pneumonia, and on investigating them he found the sputum contained an almost pure culture of the plague bacillus, the lungs being apparently the primary seat of infection. This form of the disease may again present difficulties of diagnosis, and as it is by far the most highly infectious variety, its early recognition is of great importance. The general symptoms are those of pneumonia beginning with chill, pain or tightness in the chest, high continued fever, rapid pulse and very rapid respiration, which may reach 60 or more per minute, accompanied by severe constitutional symptoms as in other forms of plague. The physical signs, however, are not in proportion to the severity of the general symptoms, as the consolidation is of the broncho-pneumonic type, although the patches are usually larger than those of ordinary broncho-pneumonia, being formed by the conglomeration of a number of smaller areas, very much as in the pneumonia of influenza, while the consolidation is frequently situated in the central parts of the lungs.

Consequently only slight loss of resonance may be found with rather coarse crepitations over the affected areas. Herpes is always absent, according to Childe, while there may be some tenderness over the superficial lymphatic glands together with tumefaction of the spleen. Buboes are absent in primary plague pneumonia, but it must be borne in mind that a secondary form of pneumonia may occur in the latter stages of typical bubonic plague. The diagnosis of primary plague pneumonia can fortunately be readily confirmed by a microscopical examination of the sputum, which is watery and sometimes very abundant; it may be streaked with blood, but only very rarely has the viscid rusty character of ordinary pneumonic expectoration. It contains enormous numbers of the typical short bipolar staining bacilli of plague, either in pure culture or mixed with various cocci. The disease is exceedingly fatal, usually within two to four days, and it is doubtful if it is ever recovered from. All the cases I myself verified by microscopical examination of the sputum during several years at the Medical College, Calcutta, terminated fatally. Chart 77 illustrates this type.

Treatment.—Unfortunately there is not much to be said on this head, as apart from general treatment directed towards supporting the strength of the patient but little can be done. Yersin's anti-plague serum promised at first to be of some value, but, as Liston has shown, no septicaemic case of plague showing as many as forty bacilli in a c.c. of blood on culture recovered after serum or any other treatment, while non-septicaemic cases frequently get well on any line of treatment. Small series of cases reported by various observers with apparently favourable results under the serum treatment, but uncontrolled by bacteriological examinations of the blood, are therefore of little or no value. A large series of 580 cases in which Choksy gave 100-c.c. doses repeatedly subcutaneously and occasionally intravenously showed a reduction of only 10.5 per cent in the mortality. A most careful test of the serum was carried out in Bombay by Liston in 222 cases with an equal number of controls, and showed a mortality of 66.1 in the serum cases and 73.4 in the controls, while he notes that the disease was modified in the direction of lengthening life and diminishing the number of bacilli in the blood, so some slightly favourable influence is produced. All observers are agreed that serum is only of use if given during the first forty-eight hours of the disease. MacConkey found that the serum maintains its powers unimpaired for some months.

Among other remedies which have been recommended are Tr. Iodine in 7-minim doses intravenously or 5 minims every three hours by the mouth, together with local applications over the bubo, Connor having reported on three cases with promising results. Liston tested the treatment in Bombay with controls in severe cases with 38 per cent of recoveries in 29 iodine cases against one of 25 per cent in 16 controls, but regards the trial as inconclusive on account of the small number of cases. In Tripoli two Italian observers

CHART 77



Pneumonic plague.

injected iodine locally in the neighbourhood of the bubo and considered that it had some effect in reducing the death-rate. Nesfield has reported favourable results from crucial incisions into the buboes followed by dressings with absorbent wool soaked in iodine lotion of the strength of 1 drachm in 2 ounces of water. Jourdain points out that an early nineteenth-century French Commission* advised mercury and iodine for plague. **Carbolic Acid** has been advised by Paton in doses of 1 grain in pill or mixture every hour together with 2 to 15 minims injected into the bubo, the urine being watched, while Todd in China has also injected 10 to 20 drops of phenol into each gland, and he gives in addition 10-grain doses of **Urotropine** every hour until irritation of the bladder is complained of, while he prefers digitalis and strophanthin to strychnine for failing heart. Tr. strophanthin in 10-minim doses every fourth hour together with 30 minims of a 1 in 1000 solution of adrenal chloride by the mouth, or hypodermically in bad cases, has been reported on favourably by Thornton.

THE BLOOD CHANGES IN PLAGUE

In 6 cases of plague examined by Acoyaina very marked leucocytosis was present, occasionally exceeding 100,000, most commonly due to excess of polynuclears, but sometimes showing a lymphocytosis instead. In a series of 28 cases recorded by me the following results were observed. The percentage of haemoglobin was higher than the normal for natives of India in half the cases, more especially in those examined early, but in the later stages it frequently falls well below the normal. The red corpuscles were also increased in over half the cases, and numbered over 6,000,000 in several instances ; these changes being of importance in differentiating the disease from other severe septicaemic conditions, in which anaemia is a marked and early sign. In one very difficult case of the carbuncular form of the disease with a mixed infection of plague bacilli and streptococci, anaemia was well marked, the haemoglobin being 58 per cent and the red corpuscles numbering 2,450,000.

The Leucocytes were found to be of still greater importance, in spite of the changes not being quite constant. With the exception of one very malignant bubonic case, proving fatal on the second day of the disease, and the septicaemic one shown in Chart 76, some degree of leucocytosis was found in every case examined during the first three days. In bubonic cases the degree was usually a slight or moderate one, in only one-tenth of the cases did the number exceed 20,000 per c.c. In the septicaemic forms from 20,000 to 60,000 were usually met with in the early stages, while in two pneumonic cases one showed 19,250 and the other only 2000. From the fourth day onwards leucocytosis is most frequently absent, especially in mild cases which ultimately recover. Thus the total leucocyte counts are similar in character to those met with in other septicaemias, namely a well-marked leucocytosis as a general rule, but there is occasional absence of leucocytosis in some very severe or very mild cases.

The Differential Leucocyte Count.—This was found often to present a peculiarity which may be of diagnostic value. In the leucocytosis of pneumonia and ordinary septic conditions there is a marked relative increase of the polynuclears mainly at the expense of the lymphocytes, so that the former number somewhere about 90 per cent and the lympho-

cytes only about 10 per cent. In the leucocytosis of plague, on the other hand, the percentage of lymphocytes may not be reduced and may even be actually somewhat high, over 20 per cent being not infrequently met with, so that the total number of lymphocytes is markedly increased. Unfortunately this lymphocytosis was only met with in half the cases examined during the first three days of the disease, so that, although its presence is an important aid to the diagnosis, yet its absence in no way excludes the presence of plague. Thus in the case of cervical bubonic plague, whose temperature curve is shown in Chart 74, a blood film had been taken as a routine measure, and on examining it—without knowing anything of the history or condition of the patient—I was at once struck by the marked and peculiar type of leucocytosis present, and as the differential count showed 44 per cent of lymphocytes, plague was suspected, and the patient, who had been admitted to the European General Hospital as probably not a case of plague at all, was at once isolated.

On the other hand, the large mononuclears are not increased in plague, but rather tend to be low. On one occasion when I first observed an increase of large mononuclears in the blood of a patient in the plague ward, malarial parasites were sought for and found, and the patient removed from the ward, and, although he was in a critical condition, recovery took place under vigorous quinine treatment. In another case which had been treated for plague for several days I found very numerous malignant tertian parasites, but here fatal coma had already set in. In all doubtful cases, then, a blood examination may be of material service, and should always be made.

BACTERIOLOGICAL EXAMINATIONS

The importance of the very early diagnosis of plague, especially at the commencement of an outbreak, when there may be no medical man available with much experience of the disease, hardly needs to be further emphasized. The urgency of the matter is often only equalled by its difficulty, and in many cases even the impossibility, of effecting a diagnosis by clinical means alone. Too much stress cannot therefore be laid on the necessity of the early use of one of the following bacteriological aids, by which definite information can rapidly be obtained in the vast majority of cases.

Firstly, a careful search should be made for any primary vesicle on the skin drained by the affected lymphatics in bubonic cases, for these are most frequently met with in the mildest, and therefore the most difficult cases to distinguish, and they are by no means rare in my experience. If found, the fluid contents should be withdrawn with a sterile syringe after carefully cleansing the skin and cultures and slides for microscopical examination made.

Secondly, if no primary vesicles are present but there is enlargement of a group of lymphatic glands, the latter should be punctured in a similar way, in order to ascertain if plague bacilli are present in them, or only staphylococci, as in cases of "climatic bubo." It must, however, be borne in mind that in the suppurative stage of plague buboes the specific bacilli may be absent and only staphylococci found. Before the suppurative stages very numerous short bipolar staining bacilli of plague will be obtained in this way. These are quite characteristic of the disease, and will enable prompt action to be taken

without waiting for the confirmation which will be afforded by the cultivation of the organisms.

Thirdly, in the absence of buboes either the septicaemic or pneumonic forms of plague may be present. If the former is suspected a small syringeful of blood should be taken from a vein in the arm and cultures made both on agar and in broth, and films stained and examined microscopically. In the later stages of the disease, which may be reached as early as the second or third day, the characteristic bipolar staining bacilli may be present in the circulation in sufficient numbers to allow of their being detected by a microscopical examination and readily isolated by culture. In making cultures from the blood from 1 to 2 c.c. should be added to from 50 to 100 c.c. of broth in a flask, to which a few drops of oil may be added in order to obtain the characteristic stalactitic growth of the plague bacillus. E. D. W. Greig, I.M.S., has recently recorded that by this means he cultivated the organism from the blood of 59·8 per cent of all kinds of plague cases examined soon after admission during the first three days of the disease, the mortality of the positive cases being 97 per cent, while that of the negative was only 43 per cent, so that this method also furnishes evidence of prognostic value.

In pneumonic cases the sputum will show innumerable plague bacilli, often in almost pure culture, and will also allow of the organism being isolated in plates, so a microscopical examination should never be omitted in any case of pneumonia which may possibly be due to plague.

Much work has been done at the agglutination test in the serum diagnosis of plague, but it has not been found to give satisfactory results, and is altogether inferior to the methods above described.

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XV. YELLOW FEVER

History.—Bérenger-Féraud, in his work on yellow fever, records an elaborate chronological account of the occurrence of yellow fever outbreaks in various parts of the world, his main conclusions being the following. As no description of the disease by writers in Europe or Africa has been found dating before the discovery of America, it is most likely a primary disease of the Western Hemisphere. The earliest probable outbreak was in 1495 among the men of Christopher Columbus after the battle of Vega Real in the Isle of Spain in the West Indies, but the descriptions of it are very imperfect. The first indisputable description was that of P. du Tertre in Guadeloupe in 1635, since which time accurate data have become more and more frequent, until during the last fifty years, or more, the disease has annually appeared in greater or less extent in the endemic areas, frequently spreading widely in most alarming epidemics, a full account of which will be found in the book referred to. The most important points to note are, that as early as 1709–90 quarantine measures were carried out with very good results in diminishing the disease, but when they were practically done away with, during the wars of the French Republic and Empire, between 1791 and 1815, it was more widely prevalent and destructive than at any other known period. Since that time, and especially after 1857, quarantine has again been vigorously enforced, being supplemented and partly superseded, subsequently to 1884, by disinfection measures based on the microbial theory of disease, which have doubtless served greatly to limit the extension of yellow fever, although they would appear to be powerless to stamp it out of the endemic area.

Geographical Distribution.—In discussing the distribution of yellow fever it is necessary to distinguish carefully between the endemic areas, in which the disease has a more or less constant yearly occurrence, and the much more extensive portions of the globe to which it may occasionally be carried from the endemic areas, giving rise to temporary epidemics, often of great intensity, but in which the disease cannot again arise without fresh importation. There has been much difference of opinion with regard to the limits of the endemic area, but Bérenger-Féraud, after a most careful study of the question, has formulated the following conclusions. The most intense seat of yellow fever is on the Atlantic coast of Mexico and Central America, from Cape Tampico in the north to Cape Gracias a Dios in the south. Next come the Greater Antilles, including the large islands of Cuba, Jamaica, San Domingo and Porto Rico, with somewhat less intense foci in the Lesser Antilles, including Martinique, Antigua, Guadalupe, etc. In these parts the disease may at any time arise without being imported, although even within this endemic

area yellow fever is very frequently carried by ship from one port to another, and it may be apparently absent for several years at a time from different islands. For this reason precautions against the infection being carried from one part to another of the endemic area ought by no means to be neglected, and will, indeed, become of increasing importance as this fell disease becomes more and more limited in its incidence, by prophylactic measures based on the knowledge acquired by recent researches.

In addition to the above-mentioned undoubted endemic areas, there are still more extensive tracts into which the disease is so frequently imported that some writers have considered that they should also be looked upon as containing endemic centres. Those about which there is the greatest difference of opinion are the coast of Brazil and the Atlantic coast of Africa from Senegambia to the Bight of Benin, some writers, such as Andrew Davidson, including them within the endemic area. It is generally agreed that up to 1849 yellow fever was not endemic in Brazil, although it had repeatedly been carried to that country. Since 1850 a series of epidemic outbreaks have occurred in Brazil, in each of which a fresh importation occurred, and up to 1876 only one year was quite free from the disease, although from 1862 to 1868 it was so much in abeyance that in no year were over twelve cases recorded. Quarantine measures have, moreover, done much to lessen its incidence, while the parts attacked have always been those trading with the West Indies, Mexico and Central America. For these reasons Bérenger-Féraud concludes that yellow fever has not become endemic in Brazil, but is always imported, while with a personal experience of the disease on the West African coast, he advances similar arguments in support of his contention that there also yellow fever is frequently an imported affection, but not actually endemic, and consequently that it cannot arise without the infection being carried there. Boyce, after seeing yellow fever in New Orleans, investigated its occurrence in West Africa, and came to the conclusion that the disease is endemic there, although frequently not recognized on account of the difficulties of differentiating it from malignant tertian malaria and the stringency of quarantine regulations causing great hesitation in diagnosing it. A West African Yellow Fever Commission was therefore appointed in 1913, to inquire into its prevalence.

In their final report of 1916 they concluded that the disease is endemic in British and other dependencies on the West Coast, while there is no evidence of its importation during recent periods from outside Africa, but it is maintained there by the existence of endemic foci; the number of cases reported not having exceeded 180 in the previous six years, although many more have probably occurred.

The next most important area to be attacked by imported yellow fever is that of the Atlantic coasts of the more southerly parts of the United States as far north as Charleston. New Orleans, with its great trade, is so frequently infected that between 1791 and 1884 outbreaks occurred there in sixty-four different years, while in twenty-seven the disease was absent, including four years when the coasts were blockaded during the War of Secession. Latterly quarantine and disinfection measures have lessened the frequency of outbreaks in the States. Those parts into which yellow fever is habitually imported extend from Charleston ($32^{\circ} 46'$ north latitude) to Rio Janeiro ($22^{\circ} 54'$ south latitude).

In addition to the countries in which epidemics of imported yellow fever are of such

frequent occurrence as those above cited, the disease is occasionally spread to places far more distant from the endemic foci. The extreme limits yet invaded are Quebec, $46^{\circ} 56'$ north latitude, and Montevideo, $34^{\circ} 54'$ south latitude, in the western hemisphere; Swansea, $51^{\circ} 37'$ north latitude, and St. Paul du Loanda, in the Congo State, 9° south latitude, on the eastern side of the Atlantic. Near the southern limits the disease has proved to be very virulent, but at most northern places attacked it was distinctly attenuated in character, while they are situated on the isothermic line of 16°C. or 60°F. mean temperature at the hottest season of the year. Fortunately, outbreaks are very rare in these higher latitudes, although serious ones have occurred in Spain and Portugal, especially in the first two decades of the eighteenth century, extending to Leghorn in Italy in 1804, and milder ones in the same areas in 1870 and 1878. In 1861 St. Nazaire in France was attacked, while in 1865 the disease was imported into Swansea from Cuba. In 1878 the disease overran the United States, no less than 132 towns being infected, and about 16,000 persons carried off; but since that date only the southern towns have occasionally been attacked, New Orleans having suffered within the last few years. In 1854 Peru was severely attacked, which is of interest as showing that countries bordering on the Pacific Ocean are not exempt, so that now that the Panama Canal is open great precautions will be necessary to prevent the tropical shores of the Pacific—and possibly even the Indian Ocean—being invaded. There appears to be no reason why the importation of the infection into the doubtless very susceptible inhabitants of those areas should not be followed by appalling epidemics, far exceeding anything yet known in the endemic areas of the disease, where so many of the inhabitants are immune, while such epidemics might be followed by the permanent settling of the disease in an endemic form in parts of the world where the temperature and other conditions are suitable.

The Recent Prevalence of yellow fever can be judged from the figures published in the *Yellow Fever Bulletin* and in the *Local Government Board Reports*, which show the following countries to have reported indigenous cases of yellow fever between 1910 and 1913 (isolated imported cases with no spread of the disease being excluded). The most numerous cases have been reported from the following nearly constantly infected South American States, Brazil, Venezuela, Ecuador, Peru and Chili, while French Guiana and Colombia also had cases, as well as Nicaragua and Honduras in Central America. Mexico also showed important and continuous infection.

Of the West Indian Islands St. Vincent was most infected, while Barbados, Trinidad, Costa Rica, Curaçao and Granada had a few cases, and Noc reports Martinique to be an endemic centre. In West Africa cases were frequently reported by the Gold Coast, South Nigeria and Senegal, and to a less extent from Dahomey, Togoland, Sierra Leone, Gambia, Portuguese Guinea and the French Congo. The West African Yellow Fever Commission in a table of the prevalence of the disease from 1900 to 1914 also record as infected the Sudan and French Guinea; Honolulu has also reported several cases and requires close watching.

On the other hand yellow fever has been stamped out during recent years as a result of the application by strong Governments of prophylactic measures based on the proof that yellow fever is carried by the *Stegomyia fasciata* (*S. callopus* of the U.S. Entomo-

logical Bureau) from the important former foci of Havana, New Orleans, Panama Canal Zone, Rio de Janeiro and Vera Cruz, which successes should encourage those states which remain a danger to the world by still harbouring this deadly disease, also to set their houses in order.

The opening of the Panama Canal has led to much speculation regarding its possible influence in spreading the disease to the Eastern countries, the danger of which Manson suggested. As the stegomyia carrier flourishes in all countries between latitudes 40° N. and 40° S. the disease would be likely to spread terribly among the highly susceptible people of the East, if the disease once gained a footing there, and the mosquitoes can be carried on infected ships for many days and to long distances. On the other hand, as Agramonte has pointed out, the Panama Canal may act as a protection and sanitary bulwark by acting as a veritable filter through which neither yellow fever nor any quarantinable disease can pass, as long as it remains under the efficient sanitary control of the United States Government.

THE ETIOLOGY OF YELLOW FEVER

Before describing the mode of infection of yellow fever, the main factors influencing the incidence of the disease must be mentioned. It is less common in young children and old people than at intermediate ages. **Race** exercises a great influence, negroes in particular being relatively immune, even when living in the United States outside the endemic area. Europeans who have long resided in an endemic area acquire a relative immunity without apparently having actually suffered from even a mild attack, although such might very easily be overlooked if sporadic. Recently arrived Europeans are most susceptible to the disease. One attack gives very marked immunity, usually lasting for life.

The Maximum Seasonal Incidence of the disease is the hottest time of the year, both in the tropics and in places in higher latitudes to which the infection may be carried, a mean temperature of 70° or over being most favourable, while frost immediately stops an outbreak. A high degree of moisture is also usually present, damp hot coast towns suffering especially.

Mode of Infection.—The great dread of yellow fever is largely due to the terrible nature of the disease, but not less to the mysterious manner in which it appears and spreads so indiscriminately. For this reason fierce discussions were carried on for several decades of the early part of the nineteenth century, between those who considered it to be contagious, and therefore advocated quarantine, and those who denied all infectious qualities, and violently opposed restrictions on trade with infected places attacked by the disease. The clothes and other effects have been generally considered up to quite recently to be frequent carriers of the infection to places at great distances, and to be able to originate outbreaks up to two or three years after contact with the germs of the disease. Hence rigorous disinfection of all things imported from an active yellow-fever centre was thought to be most essential for the protection of importing countries within the limits of the probable extension of the disease. All these difficulties have been happily resolved by

the recent experimental proof of the mosquito theory of infection, first propounded and ably advocated by Dr. C. Finlay of Havana, who produced by the bites of infected mosquitoes attacks which he believed to be mild yellow fever, and those who did not take the disease he claimed to have immunized against it. His conclusions, however, were not commonly accepted, as he failed to produce any case of typical yellow fever in all its stages.

In 1900 a United States Commission composed of Drs. Walter Reed, James Carroll, J. W. Lazear and A. Agramonte, under the leadership of the first named, were at work on yellow fever in Cuba, and finding that the bacillus described by Sanarelli was very inconstant, they began a series of experiments to test the truth of Finlay's mosquito hypothesis. Reed had been much struck by some careful observations of H. R. Carter, to the effect that after the appearance of a case of yellow fever secondary cases did not arise until two to three weeks later. Allowing for the incubation period of one to seven days, this left from nine to sixteen days for the development of the infection in such an intermediate host as a mosquito. In most of Finlay's experiments the insects had been fed on immune persons within less than that period of time after biting a yellow-fever patient. The commission having decided to try infection experiments with culex mosquitoes furnished by Dr. Finlay, Dr. Carroll first submitted himself for the trial, and suffered from a very severe and characteristic attack of yellow fever in all its stages, beginning two days after being bitten by a contaminated insect, which had been fed on yellow-fever patients up to twelve days before. Another mild attack was produced at the same time in a second subject, while shortly after Dr. Lazear contracted fatal yellow fever after allowing himself to be bitten by a mosquito while working in the infected hospital. As a result of these experiments the Commission announced that the virus of yellow fever might be carried by the *Stegomyia fasciata*, the variety used having been identified by Theobald under that name.

In 1901 the same observers carried out further experiments on a site specially constructed for the purpose, and called Camp Lazear after their lamented colleague, who had sacrificed his life for science. Here two lines of work were carried out: firstly, a continuation of the mosquito inoculations, and, secondly, experiments to see if clothes and bedding soiled with yellow fever vomit and stools could convey the infection to those protected from mosquitoes. A number of United States soldiers volunteered for these dangerous experiments which furnished most conclusive results, happily without further loss of life. Sleeping in a small mosquito-proof room with infected clothes for a number of successive nights always failed to infect, even when the bedding and clothes of the persons who had died of yellow fever were actually used and worn. On the other hand, infection was repeatedly produced by even a single bite of the right kind of mosquito, fed at least twelve to fourteen days before on a yellow-fever patient during the first three days of the disease. Further, the insects were proved to convey the disease up to fifty-seven days after being fed on an infected person, while it is possible that the time may be considerably longer, as one insect lived for seventy-one days. The incubation period varied from forty-one hours to five days, seventeen hours, and averaged three days, fifteen and a quarter hours in thirteen experimental cases. The disease was also produced by inoculating from $\frac{1}{2}$ to 2 c.c. of blood from a yellow-fever patient into a healthy one, the

incubation then being rather shorter than in the mosquito-borne infection. As yet no organism of the disease has been discovered in the blood, being probably ultra-microscopical.

These results have been since repeatedly confirmed, while Marchoux and Simond appear to have succeeded in transmitting the infection through the young of an infected mosquito. Heating the blood to 55° for about ten minutes destroys the virus. No animal, not even monkeys, have yet been infected with yellow fever. The distribution of the disease also coincides remarkably with that of the *Stegomyia fasciata*. It seems to be highly probable that the infection is only carried by the bites of this mosquito, although some instances of distant importation are difficult to explain on such a hypothesis. Measures directed against the mosquito have had most beneficial results within the endemic area in reducing, or entirely preventing, the disease in places hitherto almost invariably attacked year by year, while the good effects of fumigating vessels from infected ports is explainable by possibly infected mosquitoes being thus killed. The accurate knowledge now obtained regarding the manner of spread of yellow fever may be expected to lead to great restrictions of its incidence in the near future, for the disease is so much more dreaded than is malaria, that even comparatively ignorant people will be readily persuaded to render aid in destroying the dangerous insect pests which spread the infection.

Seidelin's Bodies.—American workers have shown that the virus of yellow fever can pass through a fine porcelain filter, as in the case of those of dengue and pappataci fevers, which Craig points out may indicate that all three are caused by a similar class of protozoal parasite, some stages of which are invisible with our present microscopical powers. This, however, does not exclude the possibility of another stage which is visible, and Seidelin has described under the name of Paraplasma flavigenum minute bodies he frequently found in the red corpuscles of the blood of yellow-fever patients, as well as in a few cases without fever, which he suggests might be carriers, while on infecting guinea-pigs with the blood of yellow-fever patients he detected the same appearances in their blood. He describes the earlier stages as extremely minute chromatin-granules with or without a faint trace of cytoplasm, and later and less abundant larger forms with abundant cytoplasm, the bodies resembling piroplasma. They require deep staining and very high magnification for their demonstration. Macfie and Johnson found similar bodies in the blood of yellow-fever patients in West Africa, and supported Seidelin. On the other hand Agramonte, the surviving member of Reed's Commission, does not accept them as parasites, while the West African Commission also rejected them, and concluded that the virus of yellow fever remains unknown. Thomson, working for the Commission, and Wenyon and Low have found similar bodies in healthy guinea-pigs in England, while they are also reported by Cropper and Drew to be common in pernicious anaemia, and in foetal guinea-pigs, and they regard them as remnants of nuclear degeneration.

Animal Infection has once been produced in a chimpanzee, while guinea-pigs are said to have been infected with the production of Seidelin's bodies in their blood and slight fever, but this is open to question. The success of prophylactic measures based on the infection being limited to man and mosquitoes makes it unlikely that any form of animal infection commonly occurs in Nature.

PROPHYLAXIS

This is based on the primary facts that infected man and stegomyia mosquitoes are the essential factors in keeping up the infection. As the mosquito carrier is an extremely common domestic one, which it is most difficult or even impossible completely to eradicate in warm climates in which yellow fever occurs, the easiest and surest way to prevent the spread of the disease is to isolate infected patients and protect them from mosquitoes; second only to which comes the reduction of the number of stegomyia in places liable to yellow fever, as it is said if they are reduced below a certain point infection will not spread. Although simple enough in theory, these measures present difficulties in practice. In the first place, in the endemic areas mild cases of yellow fever occur, which it is often impossible to detect and isolate during the first three days of the fever during which they are infective to mosquitoes, who may then infect other persons after twelve days' incubation. This is an additional reason for general anti-mosquito measures never being neglected. All patients in whom the least suspicion of yellow fever arises should at once be isolated in a mosquito-proof house or hospital, and when removed the house should be thoroughly fumigated to destroy any infected mosquitoes which may be hiding in it. If the house is a detached one this will suffice, but if not the immediately neighbouring houses should also be dealt with. According to White the stegomyia seldom goes from one house to another, and rarely travels more than 50 feet, so he found the above measures effective in New Orleans. He removes his patient from the room any time after three days, as experiments have shown the patient's blood is infective only for that period of the fever, but as this is disputed by some workers a longer time would be on the safe side. In White's opinion, in order to become infected with yellow fever, it is necessary to enter a room with a dim light where a yellow-fever patient has been at least fifteen days before, which should be easily prevented with the above precautions, if all cases are detected and properly dealt with. Compulsory notification even of suspected cases is essential for this purpose.

Mosquito Reduction is the other main prophylactic measure with a view to reducing the prevalence of stegomyia, the carrying agent, as far as possible. As the stegomyia, which is the only mosquito yet proved to carry the infection, is essentially domestic in its habits, breeding in small collections of water in close connexion with human habitations, such as earthenware pots, cisterns, roof-gutters, water-barrels, empty tins, bottles, etc., thorough house-to-house campaigns are necessary to destroy its larvae. Congreve reports the results of such a campaign under very unfavourable conditions through lack of funds at Iquitos on the upper Amazon in Peruvian territory, where other prophylactic measures could not be enforced, yet in a few months the mortality fell from 49.52 to 28.88 per mille. In all towns liable to become infected with yellow fever mosquito reduction should be regularly carried out as a precautionary measure, as once yellow fever has gained a footing it will be too late to obtain the full effects of sanitary measures. White advises that roof-gutters should be abolished in the tropics and the water allowed to fall on the ground, as in the Panama Canal area.

Screening against Mosquitoes is also an important measure, which may be applied to houses and also to ships and river steamers. The latter is most important in the case of vessels trading between infected and uninfected ports, and is now largely used. On the Amazon River completely wire-screened vessels are in use. Melville-Davidson has given careful instructions for carrying this measure out. When possible, ships entering infected ports should lie several hundred yards from the shore to prevent mosquitoes reaching them.

Fumigation of Ships and Houses to destroy mosquitoes is of great value. In the last epidemic in Cuba in 1909 in a difficult mining area houses were completely covered with large canvases and 5 lbs. of sulphur per 1000 cubic feet used. For ships sulphur dioxide is harmful to some cargoes and hydrocyanic acid is preferred by some workers, Harker's apparatus being advised for this purpose by Corlette, who also suggests adding some irritating vapour, such as mustard oil to it, to lessen the dangers attending its use. These measures are most essential when a vessel infected with yellow fever arrives at an uninfected port.

The Results of Prophylactic Measures have been most favourable where efficiently carried out. In Cuba deaths in Havana had been from 400 to 600 a year up to 1901, when preventative measures were instituted, but they fell rapidly during the next two years, and since 1904 only one death has been recorded, namely, in 1905. In Rio de Janeiro as many as 2000 deaths used to be recorded in some years, but in 1905 there were only a few and in 1906 none, and since 1909 the disease has not been seen up to 1913, at least except as in imported cases, thanks mainly to Oswaldo Cruz, the head of the Health Department.

In the more unhealthy northern parts of Brazil with very scattered population, however, satisfactory measures have not been carried out, and the disease continues to be serious. In 1905 a serious outbreak of yellow fever with 600 cases occurred at New Orleans, and a campaign against it was commenced on the lines above described by White in August, and by the end of October there was a total elimination of the disease, and of nearly all stegomyia and most of the anophelines and culicidae, in an area of 44 square miles, with a population of 335,000 inhabitants, at a cost of less than 1 cent per inhabitant per day.

CLINICAL DESCRIPTION

General Course.—Yellow fever varies so greatly in its symptoms in accordance with the mildness or severity of the attack, that it presents considerable difficulties in description. It has been subdivided by different writers into many types, most of which are named after the predominance of a single symptom, so that they need only be mentioned when dealing with that particular point. The description of the different stages in the disease is, however, of much greater importance, as their presence or absence serves to distinguish between the mild and the severe forms, while many of the most characteristic features of the affection only appear in the later period, and hence are entirely absent in the mildest cases, which never reach the second stage.

The first stage usually begins abruptly with a rise of temperature, often preceded by

a chill. It is accompanied by severe supra-orbital headache, pains in the limbs and back, staggering gait, injected eyes and flushed face. This stage lasts from two to four days, and is followed by a remission of all the symptoms, together with a fall in the temperature, which in mild cases continues until it reaches the normal on the third or fourth day. The flushed appearance and the pains disappear, and convalescence sets in without the appearance of any of the distinctive symptoms of the second stage ever appearing. These mild abortive cases terminating at the end of the first stage are very common, frequently forming over 60 per cent of all cases, and although fairly characteristic during an epidemic, they may easily be overlooked when sporadic in their incidence, and yet form foci from which a serious epidemic may arise.

A second stage appears in all but the mild abortive type just mentioned, the marked remission of the symptoms only lasting from 6 to 12 hours, while the temperature, which will have only fallen to from 100° to 101°, rises once more, and remains high with only slight morning remissions. The headache and pains reappear, with tenderness in the epigastrium, nausea and vomiting of any fluid which may have been given to allay the tormenting thirst. The eyes are now less injected than in the first stage, but begin to show a tinge of jaundice, which gradually deepens, and may reach a very high degree, colouring the skin and the urine. The pulse becomes slow in proportion to the degree of pyrexia present, and may show irregularity and a warning dropping of a beat now and then. Sleeplessness is a marked feature, with restlessness and delirium, and extreme prostration as in a typhoid condition. Albumen will now be found in the urine in variable amount which tends to increase in severe cases; at the same time the amount of fluid secreted diminishes, until there may be complete anuria. At this stage the characteristic haemorrhages from various parts of the body supervene, blood escaping from the mouth, nose, vagina, and from any abrasions of the skin, which may also show gangrenous patches. The dreaded black vomit and stools indicate similar oozing from the gastro-intestinal mucous membrane, and the patient's condition appears well-nigh hopeless. Nevertheless improvement may take place after the second stage has lasted three or four days, the temperature declines, often with copious sweating, the vomiting ceases, and sleep brings relief to the worn-out sufferer, who gradually passes into a speedy convalescence, carrying with his recovery an immunity to the terrible disease which had brought him to the brink of the grave. On the other hand, in fatal cases, rapid irregular breathing with cyanosis may end in respiratory failure; sudden syncope may release the sufferer, or complete suppression of urine with coma may produce the final dissolution.

In the rare, so-called, siderant cases the disease may be so severe as to cause death in two or three days during the first stage, without the appearance of either a remission or the typical symptoms of the later period, but such cases fortunately only form about 3 per cent of the total.

In describing the symptoms in detail, those of the primary stage will be dealt with first, then the temperature curve and pulse throughout the disease, and lastly the special conditions met with in the secondary stage; by which arrangement the general course will be closely followed, and a complete picture of the affection furnished.

Prodromal Symptoms.—Although in the majority of cases of yellow fever the onset

is quite sudden, yet in a few there may be slight preceding malaise for from three days to a few hours. This consists of general indisposition, headache, sleeplessness or restlessness, chills, loss of appetite and constipation. The subjective sensation of bad smells has also been repeatedly recorded at this period.

Onset.—Usually the disease begins quite suddenly, with a rise of temperature, often preceded by chilliness, usually not amounting to an actual rigor, and at the same time severe headache, and intense pains in the back and to a less extent in the limbs.

General Appearance.—Very early there is a striking alteration of the appearance, which is said to allow of the disease being recognized at a glance by one experienced in the disease. It consists of a brilliant injection of the conjunctiva (which is never yellow in the primary stage in spite of the name of the affection) and a flushing of the face, often amounting to an erythema, probably due to vaso-motor dilatation, and extending from the eyebrows down over the cheeks, so as to present a mask-like appearance. The lips also are congested, and later may show herpes. The tongue is furred in the centre, but red at the tip and edges, and later becomes dry and cracked.

The Skin has a similar congested look in certain parts, especially the neck, chest and abdomen, but it is little marked on the extremities. It may present an erythematous or erysipelatous appearance, and more rarely somewhat resembles measles. Another very peculiar condition of the skin in early yellow fever, to which some writers attach great diagnostic importance, is an erythema of the scrotum in the male, or the labia majora in the female, and around the anus in both sexes, which may, during the secondary stage, pass on into desquamation, the formation of bleeding fissures or ulcers, or even actual gangrene. Bérenger-Féraud considers this erythema of the genital region as almost, if not quite, constant in yellow fever, and practically pathognomonic of the disease.

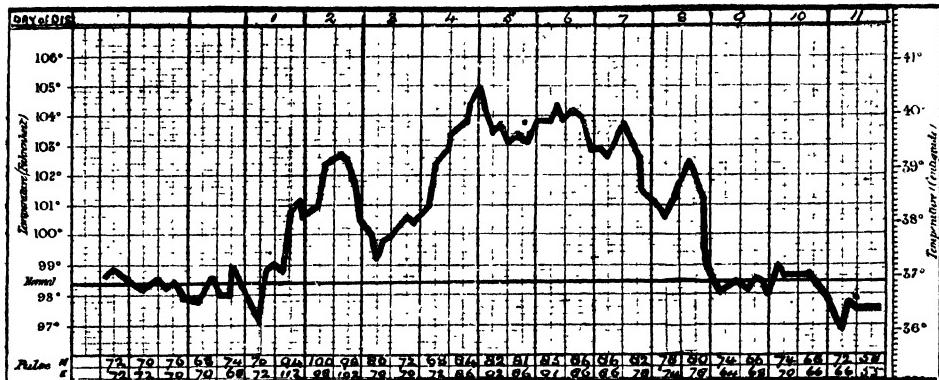
Sweats are common, especially a copious critical perspiration at the time of the remission, in mild cases terminating at that period, but less marked in those in which the temperature does not fall to normal but passes on into the second stage. The secretion has a peculiar putrid odour.

Pains.—The initial severe frontal headache has already been mentioned ; it is accompanied by pain in the eyes and often by photophobia. Pain in the lumbar region is also very constant, and may be so marked as to resemble that of smallpox. Epigastric colicky pain, greatly aggravated by pressure, considered to be pathognomonic by La Roche, appears very early with the fever, and may become unendurable. The extremities may also cause so much suffering as to amount to a hyperesthesia of such a degree as to give its name to a special type of yellow fever. One of the most definite signs accompanying the appearance of the remission which divides the two stages, is the subsidence of these various sensory disturbances and of the mental disquietude, giving rise to a period of calm, which is most deceptive in severe cases, but may be followed by sleep, which has been absent throughout the first stage.

Temperature Curve.—With the onset of the disease the temperature rises rapidly to reach 103°, 104° or more in about twenty-four hours, after which in very mild cases it

declines slowly during the next day or two until the beginning of the remission about the third day, when the fall becomes much more rapid. In the mild type the temperature now reaches normal, and remains there, so that in these cases the entire curve consists of a rapid rise to the highest point, followed by a gradual decline becoming accelerated near its end. In the medium and severe types, however, the pyrexia only falls to from 100° to 101°, as in Chart 78 on the third day of the curve, and after an interval of six to

CHART 78



Yellow fever, severe case, with well-marked remission on the third day. (Mosquito-infection case of United States Commission.)

twelve hours a further rise of temperature ushers in the secondary fever, which is very variable in degree and duration. In a somewhat mild, but typical case, the pyrexia may attain the height of the primary rise, and it lasts but three to seven days, as in Chart 79,

CHART 79



Yellow fever, moderately severe infection. (Mosquito-infection case of United States Commission.)

declining gradually at the end. In a severe case, such as is illustrated by Chart 78, the secondary fever may reach a high degree and present a continued typhoid-like character, lasting longer than in the medium cases, especially if any complications arise. Thus the temperature curve is very variable in its character and duration, the only characteristic feature being the remission, more or less marked, between the two stages of the disease. The charts are those of experimentally mosquito infected cases of the United States Commission. The West African Commission state that hyperpyaemia may occur in yellow fever.

The Pulse.—Of much greater constancy and diagnostic value is the course of the pulse in yellow fever. With the primary rise of temperature the rate of the heart-beat is considerably accelerated, reaching from 100 to 120 per minute. From this point, however, the rate steadily declines, even when the temperature remains at a high level, so that it becomes relatively slow in proportion to the degree of pyrexia, being commonly only 70 to 80 with a temperature of 103° or more. During the remission the pulse rate falls still further to the normal point, or even below it, and during the secondary rise it does not increase again in proportion to the temperature, but, on the contrary, not rarely falls to between 50 and 60, while some degree of fever remains as in Chart 79 on the fifth day of the disease. This disproportionately slow pulse is a very typical condition in the later stages of yellow fever, and as long as the regularity is maintained it is not a bad prognostic sign. If, however, intermittency and dropping of occasional beats appear, there is great danger of fatal syncope ensuing. After the temperature has finally fallen to normal in favourable cases a pulse rate of 50 or even about 40 is not very rare. In the early stages the vessels are full, although the tension is low, and the latter character becomes accentuated as the disease progresses, so much so that it may become impossible to feel the beat at the wrist some hours before death.

With the commencement of the second stage the deceptive calm of the remission vanishes, the restlessness and pains reappear, the general condition becomes graver than before, and, in addition, some or all of the following symptoms become apparent.

Jaundice.—It is only at this period that the jaundice after which the disease is named makes its tardy appearance. It is very variable in degree, from a slight yellow tinge of the conjunctiva gradually increasing up to an olive-green discoloration of the whole integument. It is thus entirely absent from the mildest abortive forms, and is not uniformly present in the recovering cases of medium intensity with a well-marked secondary stage. In fatal cases it is always present, although it is said that it may be more evident after death than during life. It commonly appears from seventy-two to ninety-six hours from the invasion, and after the disappearance of the primary erythema at the time of the remission, being evidence of the profound alteration of the blood brought about by the acute toxæmia of yellow fever.

Haemorrhages.—Closely related to, and following on the blood destruction which produces the jaundice, with the decrease in the coagulability of the blood of that condition, is the appearance of haemorrhages from various mucous membranes, and even from abrasions of the skin, which add such a lurid setting to the already sufficiently alarming picture of a severe attack of yellow fever. In the Lisbon outbreak in 1875, among 354

mild cases ending with the first stage, only 4 showed haemorrhages, but among 94 complete attacks ending in recovery, haemorrhages occurred in 85 per cent, or in a total of 18·8 per cent of all the non-fatal cases. Among 116 who died in the second stage, this symptom was noted in 76 per cent, but was absent in two very severe ones dying in the first stage. The form most frequently met with is that from the mucous membrane of the stomach, producing black vomit; this occurs in about half the total number. Next come bleeding from the mouth and nose, from the intestines producing black stools, effusions into the subcutaneous tissues, and lastly oozing from abrasions or ulcerations of the skin. It may also arise from the conjunctiva, ears, uterus or vagina in the female, or from the urethra, glans or scrotum in the male. Although many cases do recover after the appearance of haemorrhages, yet it is always a serious symptom, and may be so profuse as by itself to bring about a fatal result.

The Blood in yellow fever shows a progressive diminution of the haemoglobin and to a less extent of the red corpuscles, reaching a high degree in severe cases. The number of the white corpuscles is very variable, Pothier having found from 4660 to 20,000, the proportion of polynuclears being increased in the higher counts. The clotting power of the blood may be reduced.

Vomiting.—Although sickness does occur during the first stage of yellow fever, it is much more frequent and important in the second stage. The reappearance of the distressing thirst may be accompanied by a tendency for any fluids given to relieve it to be returned, or glairy mucus alone may be brought up, these forms being known as white vomit, for as yet the vomit contains no blood.

It is not until the second stage that the characteristic black vomit appears, varying in colour from a light grey up to coal black, in accordance with the amount of partially digested blood it contains, or if the bleeding be very copious, it may have an unaltered bright red appearance. It most frequently commences about the third or fourth day, but may only appear very shortly before death, or when not present during life it may be found in the stomach post mortem. When not containing a large proportion of mucus, it separates on standing into an upper layer of an acid green or brown fluid often containing bile, and a black flocculent sediment, which consists of blood, which has been acted on by the hydrochloric acid in the stomach and partly converted into haematin. It may contain urea in some cases, and microscopically it shows altered red corpuscles and much epithelial debris, together with various sarcinae and other saprophytic organisms. When vomiting becomes incessant, the so-called gastric type of the disease is constituted.

Bowels.—At the time of the remission the constipation of the first stage may give way to a natural action of the bowels, or somewhat loose motions may be passed, especially in severe attacks. In the second period there may occasionally be obstinate constipation, due to a paralysis of the intestines, but more frequently the bowels are loose, the stools being at first bilious in character, but later blood may appear in about 15 per cent of cases, much more commonly in fatal ones. In this late stage the amount of bile in the stools is decreased, but black partially-digested blood may give them a brownish colour. If

diarrhoea is very marked, the algid condition of the so-called choleraic type of yellow fever is produced.

The Urine.—Regular measurement and examination of the urine for albumen is of the greatest diagnostic and prognostic value in yellow fever. In the first stage there may be a sensation of heat during its passage, while in severe cases it may early be diminished in quantity by acute congestion of the kidneys. At the remission the quantity increases, and in favourable cases may become so abundant as to constitute a critical phenomenon. During the second stage the secretion is diminished to a variable extent up to complete suppression, the extreme degree always proving fatal if it lasts for fifteen to twenty-four hours: this symptom is present in 24 per cent of all fatal cases. An increased secretion during the later stages is a favourable sign.

Its reaction is always acid in the first stage, and nearly always so in the second period, but may be neutral or alkaline during convalescence. Its specific gravity and colour are high in proportion to the diminution in quantity. It presents the high colour of febrile urine in the first stage, and in the second may show any shade from yellow through orange to black in accordance with the amount of bile pigment, with or without the addition of blood, derived from the kidneys or from the bladder or urethra.

Of still greater importance is the presence of **albumen**, as the prognosis largely depends on the quantity present, moreover it has considerable diagnostic value. The date of its appearance is very variable, although it rarely appears on the first day (3 per cent), becomes more common on the second day (18 per cent), and is most usually first evident on the third and fourth (55 per cent), appearing with diminishing frequency after the fifth day. It varies from a trace up to an amount sufficient completely to solidify the fluid on boiling.

The quantity of urea excreted in the twenty-four hours is also reduced in yellow fever, and very markedly so in many of the more severe attacks, much in proportion to their severity. Granular and hyaline casts may be present at any period, and blood corpuscles or detritus in addition in the second stage.

Mortality.—The death-rate varies in different countries and epidemics. The extensive figures collected by Bérenger-Féraud show it to average from 40 to 45 per cent in the West Indies, Mexican coast and West Africa, but to be only about 25 per cent in the United States, Brazil and European countries.

Morbid Anatomy and Pathology.—The chief changes found after death, in addition to the affections of the skin already described, are congestion of the brain, hyperaemia and haemorrhages into the pericardium and pleura, mucous membranes of the stomach and intestines, the pelvis of the kidney, and sometimes also the bladder. In addition there are marked cloudy swelling and fatty degeneration of the heart muscle, liver and kidney cells, as well as jaundice of all the tissues. These lesions are all evidence of an acute toxæmic process, especially affecting the blood.

How they are brought about is not yet known, the numerous bacilli, to which they have been attributed, having been proved to be inconstant in their presence. That of Sanarelli, the best-authenticated of these, has been shown by Reed and his colleagues to be absent from the blood of most cases, and to be closely related to the organism of hog cholera. It has recently been shown that the virus in the blood of infected persons can

pass through a fine porcelain filter, so that it is probably too small to be visible with the present powers of the microscope, for it has been abundantly proved that the disease can be conveyed by inoculating a small quantity of the blood of a patient suffering from the disease into another susceptible person.

Diagnosis.—In well-marked cases of yellow fever during the known prevalence of the disease the diagnosis will be easy, especially when in the second stage. Mild sporadic cases, on the other hand, may present great difficulties, while on their recognition may depend the prevention of the development of an epidemic. Such mild cases are most likely to be mistaken for a malignant tertian malaria, especially if complicated by the haemoglobinuria of blackwater fever, the temperature curves being not at all dissimilar. The microscope is the surest means of differentiating between them, for the finding of malarial parasites, or, in blackwater fever, an increase and pigmentation of the large mononuclears, will enable those diseases to be recognized. The pulse is also a very important guide, for it is nearly always rapid during the pyrexia of malarial fever, but soon becomes slowed down in yellow fever. Relapsing fever is said also to be easily mistaken for yellow fever, especially the bilious typhoid-like fever, but here the pulse is always very rapid during pyrexia ; while an examination of the blood will show the presence of the spirillum and also a leucocytosis, instead of the low leucocyte count of yellow fever. Further, in both the above diseases albumen is rarely found in the urine, except during haemoglobinuric complication, while it is present, as a rule, in yellow fever after the second day. Dengue is another disease for which mild cases of yellow fever are said to be mistaken, but here the pains are more marked in the limbs and joints, and albuminuria is again absent. Seven-day fever in its early stages, with its rapid rise of temperature, followed by a gradual decline with a slow pulse, might easily simulate a very mild abortive yellow fever, should it be found to prevail in the areas affected by that disease, as is not very improbable considering its liking for hot coast towns. In countries where yellow fever is rarely seen a severe case might excusably be mistaken for acute yellow atrophy. The most important diagnostic signs are the following :—

A falling pulse rate accompanied by a rising or horizontal temperature curve, known as Faget's sign from the physician who described it as early as 1870 in New Orleans ; albuminuria present on the third day and lasting as long as the fever, but disappearing with it and accompanied by numerous casts in the urine ; epigastric sensitiveness on pressure ; almost invariable absence of enlargement of the spleen ; absence of leucocytosis, although the proportion of polynuclears may be rather high at first, and the later stage as a mononuclear increase, and the congested appearance of the conjunctiva usually, but not always, with jaundice in the later stages. A rapid diminution of the urea and nitrogen in the urine is also laid stress on by Villuendas and is worthy of further study.

Treatment.—Like some other acute specific fevers, the number of drugs which have been extolled in the treatment of yellow fever is in inverse proportion to their actual value, for none of them can be relied on to control its course in any way. The first indications, on suspecting a patient to be suffering from this disease, is to place him in bed under a mosquito curtain, both to prevent the infection being spread by the stegomyia and to afford the sufferer the best chance of recovery ; for it is worthy of note that none of the

United States Commission's experimentally infected patients, except Dr. Lazear, died of the disease, all being kept at rest in bed from the appearance of the first signs. In the early stage a mild laxative, such as castor oil, is indicated, or if vomiting be present, 5 to 10 grains of calomel is preferable. The pyrexia should be controlled by cold spongings. Quinine appears to be of little or no value in this disease, while such depressing drugs as antipyrin, etc., should be avoided on account of the weakness of the heart. Alkalies are very generally recommended in all stages, Sternberg's method of giving hourly three tablespoonfuls of a mixture containing 75 grains of bicarbonate of soda and one-sixth of a grain of perchloride of mercury in one pint of iced water having been specially well reported on. Some recent writers advise the omission of the perchloride of mercury from Sternberg's mixture. Thomas gives 15- to 30-grain doses of sodium bicarbonate every three hours until the urine is neutral or alkaline, which in view of the value of this drug in preventing anuria in cholera, appears to be a sound line of treatment. Ice-bags over the head and stomach relieve headache and sickness respectively. The old purgative treatment has largely died out, and after a preliminary purge the bowels may be kept open by sodium chloride or sodium sulphate enemata. The temperature may be controlled by sponging every two to four hours whenever the temperature is above 102° F. Baths may be of use for persistent high fever if sufficient skilled nursing is available. Haemorrhages are difficult to treat on account of the tendency of all drugs to be rejected by the stomach in such severe cases. Adrenalin and calcium chloride are most generally recommended, while subcutaneous or intravenous injections of horse serum which increases the coagulability of the blood would be worthy of trial. Morphine has been advised for restlessness, but should be avoided unless the urinary flow is free. For cardiac weakness Tr. strophanthine and caffeine-sodio-salicylate are best.

Feeding is a great difficulty owing to stomach irritability. Thomas and others advise that no food should be given during the first three or four days, but it is essential to get large quantities of fluid into the system to maintain the circulation and action of the kidneys and eliminate toxins. From two to three litres given at regular intervals are advised in the form of a weak alkaline water or sodium bicarbonate solution. If this amount cannot be taken by the mouth and retained it must be given either as saline enemata, with which bicarbonate of soda might well be combined as in my cholera treatment, or by subcutaneous or intravenous injection. Glucose in 5 to 10 per cent solution has been suggested by Balfour for hepatic deficiency given either by the mouth or the rectum, and I have given it largely as a useful food in cholera for keeping up the strength of the heart during the necessary period of starvation; so it should also be of use in yellow fever. Most authorities are agreed that alcohol should be strictly forbidden in yellow fever on account of the already lowered coagulability of the blood, but Thomas recommended iced champagne for continued sickness. Ice to suck might be equally effective.

During convalescence great care is necessary with regard to the diet to avoid recurrence of the vomiting initiating a fatal relapse. Thomas begins on the fourth day with milk and lime water, toast or barley water in small amounts, continuing with chicken jelly, raw eggs and fish. The patient should be kept recumbent for some days and sudden exertion avoided for a considerable time on account of the weakness of the heart muscle.

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XVI. HEATSTROKE—SUNSTROKE AND EFFECTS OF HEAT

Nomenclature and Synonyms.—In the older Indian Army returns great confusion was caused by classing cases as “heat apoplexy” with cases of true apoplexy due to cerebral haemorrhage, etc. As in heatstroke there are no constant gross lesions of the brain the term “heat apoplexy” is a bad one and should not be used. “Insolation” and “coup de soleil” are other synonyms for these conditions. Norman Chevers discussed this question and concluded that the term heatstroke was least open to objection on account of many cases occurring without actual exposure to the sun’s rays or even occasionally during the night. Sir P. Manson divides these cases into three classes. Firstly, heat exhaustion, characterized by syncope brought about by exposure to high temperatures. Secondly, sun-traumatism, or sunstroke, a somewhat ill-defined class shading off from a first subdivision of syncopal heat exhaustion into a third of true heatstroke, and due to exposure to the direct rays of the sun, often with insufficient protection of the head and spine. It occurs either in the form of sudden syncopal attacks, which may be immediately fatal, as in cases of soldiers marching or fighting during great heat, or it is accompanied by fever and loss of consciousness as in true heatstroke. Thirdly, true heatstroke, which he prefers to call by the old term “Siriasis” as not embodying any etiological theory.

From an examination more especially of the Indian literature of the subject, it appears to me that there are two broadly different conditions embraced by these terms. First, those in which a syncopal attack occurs as a result either of exposure to the direct rays of the sun or of hard labour during great heat, such as in the stokeholds of steamers in the terrible moist temperature of the Red Sea, or Persian Gulf more especially. In these cases there may be no marked elevation of the body temperature, and recovery nearly always takes place under suitable treatment, with or without some permanent mental injury, this occurring particularly in those produced by the sun’s rays.

Secondly, we have the true heatstroke in which hyperpyrexia, with acute congestion of the lungs, comes on very suddenly, usually without any actual exposure to the sun’s rays. These cases only occur under very trying atmospherical conditions, due either to very excessive dry heat, or to somewhat lesser degrees of moist heat, which are more difficult to bear than much of higher dry temperatures. For these cases the old-established term heatstroke will be retained for reasons which will appear. In the first class it is faintness due to heart failure under special stress which takes place. In the second, it is essentially loss of consciousness due to hyperpyrexia, the precise cause of which is attributed by different writers either to exposure to excessive heat, producing in some

way not yet fully understood, failure of the heat-regulating mechanism of the body, or to the toxins produced by a hypothetical microbe. Fiske studied 1507 cases of disability due to heat in the United States Navy from 1886 to 1910, and classed 64 per cent of the cases as "heat prostration" apparently of the syncopal form, 34 per cent as "thermic fever" and 4 per cent as "insolation," the last two being apparently heatstroke proper. Duncan also found the syncopal form in the most common variety, although it is much less serious and more quickly recovered from than the hyperpyrexial condition. The syncopal form more commonly occurs as a result of direct exposure to the sun, or **sunstroke** proper, and usually begins with intense headache and great intolerance of light, which may last for a long time or even be followed by unconsciousness according to Duncan, but usually it gradually abates. From 1912 to 1915 the cases in the British Army in India have been divided into heatstroke and sunstroke, and the returns for those years show a death-rate from heatstroke of cases admitted to hospital (the figures of those dying before admission do not appear to have been published since 1910) of 15.27 against one of 6.71 among the sunstroke cases, two-thirds of which were returned in 1914. In 1912 there were 61 cases of sunstroke with 1 death, and in 1915, 35 cases with no deaths, clearly showing this condition to be much less serious than true heatstroke.

HISTORY OF HEATSTROKE IN INDIA

Annesley in 1828 describes fevers with affection of the brain occurring in Madras during very high temperatures and caused by exposure either to the sun or to a high range of temperature, especially among new arrivals. Twining in 1835 describes a continued fever of the dry hot season, caused by exposure to the sun or violent exercise in hot weather, and treated it by venesection, cold douching and purging. Mackinnon in 1855 describes "ardent fever" as affecting especially new arrivals in the United Provinces during the dry hot months, and sailors on the Hugli River at Calcutta, with death from coma. He thought that bleeding was used too freely in the disease, that it was a fatal measure in alcoholic subjects and those due to direct exposure to the sun, but that cold affusions to the head had a wonderful efficacy. Francis Day, in his elaborate epitome published in 1858 of the Indian literature of fevers, says that non-malarial fevers constitute 46 per cent of all fevers among Europeans in the Madras Presidency, but only 1 per cent among natives. He classes them as "ephemerals," "common continued fever" and the more severe "ardent continued," culminating in "insolation" caused by long-continued tropical heat, and predisposed to by alcohol. Scriven, who describes the fevers of Calcutta in 1857, says that sun fever is of two kinds, one due to the direct action of the sun's rays, the second to prolonged heat in the shade producing coma, predisposed to most strongly by habitual drinking, and undoubtedly a fever. They occur only during high atmospheric temperatures and show hyperpyrexia. He notes a tendency to a very slow pulse soon after the cessation of the pyrexia, one of 40 to 52 beats a minute being noted in 12 out of 28 cases, all of which recovered. In 1859 Thomas Longmuire carefully described 16 fatal cases of "heat-apoplexy" occurring at Barrackpore (fifteen miles north of Calcutta) in British troops between May 23 and June 14 of that year, although 10 of them had not been exposed to the sun during the day of the attack. Three were attacked during

very soon after sentry work, but 5 were affected while in hospital for other diseases. Only 1 was intemperate. The hours of the attacks were, in 10 cases between 2 and 5 p.m., 5 more between 5 and 9.30 p.m., none during the night, and the remaining 1 at 11 a.m. in a man admitted for fever one hour before. He remarks: "Whatever other causes may have been in operation to produce these attacks, it is impossible to avoid associating their particular appearance at these hours with elevated temperature. The thermometer generally indicated the maximum temperature of the twenty-four hours to be at about 4 p.m., but during most of the period in which these cases occurred the variation in the thermometric range was very slight from 2 p.m. to sunset. Even for some hours after sunset the temperature scarcely declined at all." Under meteorological notes he writes: "The weather throughout the period included in the return was excessively hot, sultry and oppressive. The highest temperature, as indicated by a thermometer placed in one of the hospital wards, varied from $91\frac{1}{2}$ ° to $97\frac{1}{2}$ °. About the time 7 of the cases occurred the thermometer was standing at 97° , or above, and above 95° F. at the time 12 of the cases occurred. The first heavy fall of rain on June 11, which reduced the air temperature, may be said to have put a stop to the cases of apoplexy, only 1 case occurring three days later." One-third of the cases and half the deaths took place in one barrack, which was the worst ventilated and punkered. He concludes: "It seems clear that prolonged nervous exhaustion, and a contaminated atmosphere, acted as predisposing causes in those attacked and that, in most of these instances, a certain increase of the average prevailing temperature sufficed to act as the exciting cause of development of the apoplectic symptoms."

J. H. Butler also reported a number of cases of heatstroke at Mian Mir in June 1859, occurring when "the weather was most sultry and oppressive—there was that close dense condition of atmosphere, synchronous with which attacks of apoplexy, insolation or heat-apoplexy, where troops are crowded together, always more or less obtain. The thermometer ranged, between sunrise and sunset, from 94° to 102° . It has been repeatedly observed that, when the thermometer ranges beyond 98° in crowded barracks, cases of apoplexy almost invariably obtain. On the two days when the air temperature was highest, namely, that from 99° at 10 a.m. to 100° at 4 p.m. and from 98° to 102° , 16 and 7 cases respectively were admitted. Heavy rain fell two days later and the outbreak ceased at once with the rapid fall of temperature. A few scattered cases occurred later on, also on very hot days, the rains at Mian Mir being very scanty. There was no fatigue or interference as a cause of these cases, but great overcrowding of the barracks, those which were most overcrowded, least ventilated, and worst provided with punkas furnishing most cases." He concluded: "I believe that the proximate cause of this outbreak of sickness was excessive heat of the atmosphere, acting upon the nervous system of the young and unseasoned soldier."

These two outbreaks may be taken as typical of the conditions under which heatstroke occurred in two places with such widely different climates as Barrackpore in Lower Bengal and Mian Mir in the Punjab, yet in both they were intimately associated with unusual heat, and both terminated by heavy rain, which rapidly reduced the temperature. The occurrence of almost all the attacks at the hottest time of the twenty-four hours is noteworthy, as it is totally at variance with the emphatic statement of a recent supporter of the microbic theory of the disease.

ETIOLOGY OF HEATSTROKE

Definition.—By heatstroke is meant a condition of hyperpyrexia and loss of consciousness occurring during exposure to excessive heat for a longer or shorter time, without necessarily subjection to the influence of the direct rays of the sun.

It thus may take place in the stokehold of a steamer on account of the great heat from the furnaces, and this may even occur in a temperate climate, as recorded by L. F. O'Grady at Plymouth, although much more commonly it occurs in a hot one. In tropical ports it frequently is found among sailors while resting in the afternoon in their sleeping quarters, especially in iron ships. People are occasionally struck down in the tropics during hot stifling nights in India while in their beds, or in railway carriages during the heat of the day.

It has, however, been suggested that the disease may really be due to the toxins of a microbe and not simply to heat exhaustion. The main ground on which this theory has been built is a statement that the distribution of the affection in different countries shows no absolute relationship between the actual degree of heat experienced and the frequency of heatstroke cases, which may be rare in one country with very high maximum temperatures, and yet more common in another where extreme high degrees are never reached. It is also stated by Samson that most of the cases occur at night, and not during the hottest part of the day.

This argument, however, leaves out of account a most important factor, which has not received the attention it deserves. Any one with prolonged personal experience of different tropical climates is aware of the fact that the exact degree of temperature is only one element in rendering a place more or less trying to the heat-regulating mechanism. A second, and nearly equally important one is the degree of moisture in the air. Thus a temperature of 100° F., with a high degree of moisture in the atmosphere, is much more unbearable than a temperature of 110° F. with a very dry state of the air.

The explanation of this well-known fact is an obvious one. The principal factor in keeping the body heat down to the normal temperature, when the atmosphere is above that point, is the great amount of heat dissipated by the evaporation of the insensible perspiration, and in a hot dry atmosphere this evaporation takes place so rapidly that no visible perspiration appears on the skin, which feels dry. The great loss of fluid due to this insensible perspiration is evidenced by the thirst and scanty secretion of urine experienced under such conditions. On the other hand, in a less hot, but much moister, atmosphere the sweat cannot evaporate as readily as it is secreted by the skin, but pours from the surface in large drops, and the system experiences much greater difficulty in keeping down the body heat under such conditions.

It will be clear from the foregoing that both the actual air temperature and the moisture it contains must be taken into consideration in estimating the liability of the climate of any given place to induce exhaustion of the heat-regulating mechanism, and so possibly by itself to be actually the exciting cause of the hyperpyrexia of heatstroke.

Physiological Experiments lend strong support to the importance of the moisture in the air as well as the actual temperature. Thus Pembrey states that a dry temperature

of even 115° to 126° C. can be stood by man without discomfort for fifteen minutes, but when the wet-bulb thermometer exceeds 88° to 90° F. (31° to 32° C.) dyspnoea and exhaustion rapidly ensue even at rest, and if muscular work is performed a wet-bulb reading of 80° F. (26.7° C.) causes distress, but a movement of the air of two miles an hour permits a wet-bulb reading of 93° F. (33.9° C.) to be borne. Segale showed that in the case of guinea-pigs a dry heat of 39° C. can be borne indefinitely, but a moist heat of the same temperature rapidly kills the animals, which actually absorb heat from the atmosphere. Shaklee experimented with monkeys in the Philippines and found that they could readily be killed by exposure to the sun in Manilla, especially if the humidity was high and the atmosphere still, but they could gradually be acclimatized to a considerable extent. A dose of atropine, however, by stopping perspiration led to the death of an acclimatized monkey. Healthy white men could also be acclimatized if on a suitable diet and gradually introduced to work in the sun. Pembrey also found that an experimental march of seven miles at Aldershot caused a maximum rise of the rectal temperature of 2.3° on a warm day with a wet-bulb reading of 67.5° F. and of only 1.6° F. on a cold day with a reading of 38° F. in the same men. All these facts illustrate the importance of paying attention to the wet-bulb reading as well as to the actual air temperature.

India as a Field for the Investigation of the Effects of Climate on the Incidence of Heatstroke.—In order to investigate the effects of different climatic conditions on the incidence of heatstroke it is necessary to obtain data of both the occurrence of cases, and the meteorological records at the same time, in a number of places presenting different types of climates. India offers peculiarly favourable circumstances for such an inquiry owing both to the incidence of heatstroke in the British Army and the fact that meteorological data are available for a large number of places. Moreover, India presents a series of different climates, probably unsurpassed in number in an equal area in any other part of the world. They vary from the temperate climate of the hill stations on the one hand, up to the extreme dry heat of the Punjab and the Sind and the notoriously trying and very damp heat of Lower Bengal, Madras and Bombay. In all parts of this country British troops are stationed. Through the kindness of the officers of the Royal Army Medical Corps, I have been able to obtain records of the exact dates of occurrence of all the heatstroke cases in nearly every complete British regiment for the years 1904, 1905 and 1906; again, through the kindness of C. W. Peake, Meteorologist, Calcutta, the temperatures, moisture, rainfall and wind records of the same places on the same dates have been put in my hands. Further, I have been able to study all the cases which have occurred in the European Hospital, Calcutta, during several years. The results of an analysis of this material throw much light on the subject; they also disprove, as far as India is concerned, nearly every statement on which the theory that heat is the cause of the affection has been disputed by the microbe theorists. Tables have been worked out separately showing the fatal cases and the total cases, as the former are likely to be somewhat more accurate than the latter, which probably include a few cases of other diseases wrongly diagnosed as heatstroke.

The Monthly Incidence of Heatstroke.—Table XXXIX., Part I., shows the monthly incidence of 60 fatal cases of heatstroke in India. Every single case occurred during the

hot months from May to September, while three-quarters of them took place during the two hottest months of the year, namely, June and July. No less than half the cases occurred during the excessively hot month of June, while another quarter took place in the next hottest month, namely, July. Moreover, the maximum occurrence in different parts of India is in the hottest months. Thus nearly all the cases which were recorded in July took place in the Punjab, where the monsoon is scanty, and July is the hottest month. On the other hand, in the United Provinces of Agra and Oudh, and in the Central Provinces, the great majority of the cases occurred in June, the hottest month there, owing to the south-west monsoon setting in by July in those parts.

Table XXXIX., Part II., shows similar data for all the cases returned as heatstroke. It shows the same distribution in a slightly less pronounced manner. Thus 95 per cent

TABLE XXXIX.—MONTHLY INCIDENCE OF HEATSTROKE IN INDIA

	January.	February.	March.	April.	May.	June.	July.	August.	September.	Oct.-ber.	November.	December.
PART I.—FATAL CASES.												
Total	7	31	15	4	3
												60
PART II.—TOTAL CASES.												
Punjab	5	73	122	24	3
United Provinces and Bengal	3	2	11	55	22	17	10	1
Central India	1	10	16	1
Bombay	2	4	7	9	7	4	..	1	1
Madras	1	1	1	2	3	2	10
Burma	2	2
Total	0	1	6	8	37	156	152	45	13	2	1	3
												424

of the cases were returned in the hot months of from May to September, and 2 per cent more in the next hottest month of April. No less than 72 per cent occurred in June and July, the great majority of the cases in the latter month again being recorded in the nearly monsoonless Punjab. Most of the few cases returned in the remaining months were in Madras and Bombay, where there is no really cold weather, and it may be very hot at almost any time of the year. Further cases of malaria with cerebral symptoms are sometimes mistaken for heatstroke, while in a few of the returns the distinction between heatstroke and those in which actual exposure to the direct rays of the sun, which should therefore be classed as "sunstroke," does not appear to have always been carefully made, and thus the return of such a small number as 3 per cent of the cases in other than the hottest months of the year can be readily accounted for.

The data for the last three available years just given are practically identical with an analysis of all the cases in the British Army in India for the years 1890–95, which are tabulated in the Report of the Sanitary Commissioner with the Government of India for

the year 1897, in discussing which that officer concluded : " It is a matter of common knowledge that heat, sufficient in degree and properly applied, can disintegrate the tissues and even cause death without the necessary intervention of any microbe. When it is found, therefore, that heatstroke is commonest in the three hottest months and in the geographical groups where heat is fiercest, it seems not unlikely that *heat pure and simple is the chief factor, other than those supplied by the patient, in producing the stroke.*"

Degrees of Heat and Moisture associated with Heatstroke.—Next we may consider the moisture and temperature of the air at the time of the occurrence of heatstroke cases. The data available are the daily maximum, minimum and mean temperatures, and the percentage of saturation of the air with moisture. The strength and direction of the wind have been also studied, but, except that most cases occurred on calm days, they proved to be of less importance than the other factors. As the diurnal variation of the temperature in the hot weather in the parts of India where most cases of heatstroke occur averages about 20° F., while it is *prolonged* exposure to a temperature approaching blood heat rather than a shorter time in very excessive temperatures which is most exhausting to the human system, the daily mean temperature appears to be the most useful datum to study. The cases have therefore been classed into groups according to the mean temperature of the twenty-four hours on which they took place, and further subdivided as regards the percentage of saturation of the air with moisture the results are shown in Table XL. The fatal cases have also been separately classed to show the maximum temperature of the day on which they occurred, as this will be very near to the actual air temperature when the great majority of the attacks happened, because, as is shown in Table XL1., as a matter of fact three-fourths of the patients were admitted to hospital during the hottest period of the twenty-four hours. As a glance at the table shows that heatstroke occurs at a much lower mean air temperature when a high degree of moisture is present than when the air is dry, the percentage of cases under each 10° of moisture has been worked out for the different mean temperature periods shown in the table in order to bring out this important point more clearly.

Taking first the fatal cases, we find that only 1 occurred with a mean temperature below 85°, and 7 more with one between 85° and 89° F. In all but one of these the moisture was over 70 per cent of saturation, a very damp atmosphere, which must greatly interfere with the free evaporation of perspiration, by means of which the body is so greatly cooled in tropical climates. A mean temperature of 85° to 89° F. corresponds with a maximum one of about 95° to 99°, or about blood heat, so that fatal cases of heatstroke scarcely ever occur until a maximum air temperature of about the human body is reached, and then only when a high degree of moisture is also present.

When the maximum temperature reaches 100° to 103° heatstroke is not uncommon with a percentage of moisture between 60 and 70, but only three cases occurred with still drier atmospheres of that degree of heat, while with the corresponding mean temperature of 90° to 93° only 1 case took place with a degree of moisture below 61 per cent of saturation. When, however, the mean temperature reaches between 94° and 98°, and the maximum between 104° and 108°, then heatstroke cases occur with a drier atmosphere, although they are still most frequent with over 50 per cent of moisture. With yet higher

temperatures of over 98° mean, or 108° maximum, heatstroke cases are comparatively frequent with dry atmospheres, such as are indicated by 30 to 50 per cent of moisture.

TABLE XL.—DEGREES OF TEMPERATURE AND MOISTURE ASSOCIATED WITH HEATSTROKE

PERCENTAGE OF MOISTURE IN THE AIR

	-31	31-40	41-50	51-60	61-70	71-80	81-90	+90	Total.	Percentage.	
PART I.—FATAL CASES.											
Maximum air temperatures.	-95	1	3	3	..	7	11.3	
	95-99	1	2	1	..	4	6.5	
	100-103	..	1	2	..	8	1	..	12	19.4	
	104-108	2	2	1	5	4	2	..	16	25.4	
	+108	1	7	9	2	4	23	37.3	
Mean air temperatures.	-85	1	..	1	1.4	
	85-89	1	4	2	7	11.3	
	90-93	1	6	3	1	..	18.0	
	94-98	2	5	5	3	8	1	..	24	38.7	
	+98	1	4	8	3	3	19	30.6	
PART II.—TOTAL CASES.											
Mean air temperatures.	-85	1	1	5	3	2	3	15	4.1
	85-89	6	11	13	1	31	8.6
	90-93	3	1	4	5	20	14	4	1	52	14.3
	94-98	12	27	26	29	64	16	1	..	175	48.2
	+98	8	20	30	15	17	90	24.7	
Percentage	6.3	13.2	16.8	13.8	39.9	12.1	5.5	1.4	..
Mean air temperatures.	-85	2	2	4	7	10	60
	85-89	5	25	65	20
	90-93	13	2	7	10	18	31	20	20
	94-98	52	56	42	58	57	36	5
	+98	35	42	49	30	15

Fortunately such high temperatures do not occur combined with a moist atmosphere in places in India where European troops are stationed. Possibly they might be met with in the stokeholds of ships in such very damp hot climates as that of the Red Sea, where heatstroke is so common, and observations on the moisture, as well as the temperature, under such conditions, would be of interest.

The figures in the second part of Table XL. of the total number of 363 cases of heatstroke in the British Army in India show results exactly parallel to those of the fatal cases just detailed. In only 4 per cent was the mean temperature below 85° F., and in several of these the reading was due to a low minimum temperature produced by heavy rain or a dust storm occurring after the attack had ensued, the maximum temperature at the time of the onset of the hyperpyrexia having been about blood heat or higher. In 8.6 per cent the mean temperature was between 85° and 89°, almost every case happening

with a mean daily temperature under 90° being associated with an air moisture of over 60 per cent. In the remaining 87 per cent of the cases the mean temperature was 90° or more, and the maximum one over blood-heat, while in 73 per cent of the total cases the mean temperature was 94° or more, which is within a very few degrees of the normal body temperature, the long continuance of which, often for days together, must put a very great strain on the cooling mechanism of the human system.

The last part of Table XL. showing the percentage of cases occurring at different mean temperatures, classed under each 10° of moisture in the air, brings out well the importance of the last factor. Thus, with over 90 per cent of moisture, 3 out of the 5 cases took place with a mean temperature of under 85°, while with from 81 to 90 per cent of moisture, three-fourths of the cases took place with a mean temperature not exceeding 89°. On the other hand, with a moisture between 61 and 70, 72 per cent of the cases occurred at a mean temperature of over 94°, and with a moisture of only from 40 to 50, just half the cases took place with a mean temperature of over 98°. With still drier atmospheres the proportion at different temperatures remains about the same, as the hyperpyrexia is now no longer largely dependent on interference with the free evaporation of sweat, but can be produced by such great degrees of heat without the aid of that factor.

We may conclude, then, from this study of the combined effects of heat and moisture on the incidence of heatstroke cases, that the occurrence of the disease may readily be explained, on purely physiological grounds, as a result of either very excessive degrees of mean heat combined with a dry atmosphere, namely, those of about body temperature or above that point, or of somewhat less excessive temperatures combined with such considerable percentage of moisture in the air as will materially interfere with the cooling effect naturally produced by the free evaporation of perspiration from the body surface. Thus by taking into account the degree of saturation of the air with moisture as well as the actual temperature, the incidence of heatstroke is simply accounted for without falling back on the hypothesis of some undiscovered microbe as its exciting factor.

Hour of the Attack.—There is another point of view from which this subject may be considered. If heatstroke is due to some hypothetical microbe it might reasonably be expected that the time of the sudden onset of hyperpyrexia and unconsciousness would be fairly uniformly distributed over the twenty-four hours. If, on the other hand, the affection is due to the physiological effects of heat, then the majority of the attacks should take place during the hottest portion of the day. Table XLI. gives the data of those

TABLE XLI.—HOUR OF ONSET OF HEATSTROKE

	Cases.	Percentage.
Noon to 4 P.M.	22	35·5
4 P.M. to 8 P.M.	24	38·7
8 P.M. to midnight	5	8·1
Midnight to 4 A.M.	0	0·0
4 A.M. to 8 A.M.	7	11·3
8 A.M. to noon	4	6·4
		74·2
		25·8

cases in which the hour of onset or admission to hospital was noted in the present series. It appears from this that almost exactly three-quarters were admitted between noon and 8 P.M., while only 8 per cent occurred between 8 P.M. and 4 A.M. The remaining 18 per cent were admitted between 4 A.M. and noon, mostly in the early morning, having been attacked during the night, as occasionally occurs. The great preponderance of cases in the hot afternoon is thus very marked, and is in accordance with a physiological exciting factor due to the heat and against the microbic theory, and disproves the statements of its supporters as regards India.

In my Calcutta series the exact hour of the onset of the symptoms was noted in 13 cases. In no less than 9 of these the attack occurred between 3 P.M. and 5 P.M., while in 12 out of the 13 it took place between 1 P.M. and 8 P.M., and in the remaining case at 10 P.M. Longmore's experience already quoted is also the same.

Distribution of Heatstroke Cases in India.—It has already been mentioned that most of the cases in the British Army occur in the hottest provinces and during the hottest months. Sambon, however, states that "its endemic regions are strictly limited. Like yellow fever it prevails only in the lowest regions or coast districts, or in the valleys of great rivers." He further states that it is found in the great low plains drained by the Ganges and Indus, but is unknown on the plateaus. He concludes that its distribution is capricious and irrespective of heat. As Sir Patrick Manson has adopted these statements in his widely read work on tropical diseases, and further remarks that the disease is never found at a height above the relatively low altitude of 600 feet, it will be worth testing them in the light of the data of the three years' records I have collected from European troops in India.

In the first place, out of 421 cases (including some for which meteorological data were not available) in my lists I find that only 4 occurred in Bombay and 7 in Madras in the three years, in spite of full regiments being quartered in those places. They are also uncommon in soldiers in Calcutta, so that the disease is very far from being specially prevalent on the low coast towns of India, as yellow fever is in America. It is true that the majority of the cases in the military returns occur in the huge areas drained by the Ganges and Indus rivers, because these are both the hottest parts of India and those in which the great bulk of the British Army is stationed. To compare these dry, hot areas with the damp coast-line from the climatic point of view is, however, absurd; for the influence of these rivers on the climate of the enormous areas they drain may well be compared to the cooling and damping effect of the evaporation of one drop of water in a large and highly heated hothouse. Moreover, cases occur in stations many miles distant from the large rivers of the United Provinces and Punjab, while they are very rare in the much damper Brahmaputra valley of Assam, which does not show such high temperatures as the Ganges and Indus plains.

Elevation.—The statement that cases do not occur on the plateaus of India or above a height of 600 feet is equally untrue. They are very common at Rawal Pindi, at a height of over 1500 feet, a number of cases having been seen by me there in the hot weather of 1894. Again I have received returns from six stations, each with a complete British regiment, in the plateau of Central India and the Central Provinces, and every one of them

returned a number of cases of heatstroke during the last three years, 14 having occurred at the one station of Kamptee, the cantonment of Nagpur. In fact, cases were reported from five stations at over 1500 feet, but with very hot climates, while *no less than 71 per cent of the 424 cases occurred at over 600 feet elevation above the sea.*

It has also been stated that heatstroke does not occur in some very hot places with temperatures up to 120° or over, such as on the north-west frontier of India. This is true of the British Army returns for the very good reason that British troops are not ordinarily stationed at such places. When, however, they have to be sent there in wartime, cases of the disease are very prevalent among them. Thus, in 1898, European troops were sent to Bunnu, 120 miles west of the Indus, during the hottest season at the end of June, and numerous cases of heatstroke, many of them fatal, occurred, some of which I saw myself. Several of them were in men while in camp and not undergoing severe fatigue.

To sum up, with regard to the distribution of heatstroke in India, the principal statements on which Sambon and Manson rely in support of their theory that the disease is not due to heat, but to a hypothetical microbe, are either untrue or can be quite well explained by the simple heat theory of the causation of the disease.

The Distribution of Heatstroke Cases in relation to Heat-Waves.—I have also worked out the daily distribution for each station of all the cases in the two months of June and July, during which 72 per cent of the total occurred, in relationship to the temperature and moisture conditions for three years. The following are the data of those places and provinces where an unusually large number of cases of heatstroke occurred.

In 1904, in the very hot station of Multan, 8 cases of heatstroke occurred between June 9 and 21. During this period the mean temperature varied from 97° to 102° and the maximum from 107° to 114°, and the moisture from 42 to 67 per cent of saturation. On June 22 the maximum temperature suddenly declined to 104° and remained at about that point, and at once the cases of heatstroke ceased. The only other cases were 1 in July and 1 in August, both with specially high temperature or moisture.

1905 was an exceptionally hot year, and also showed an unusually large number of heatstroke cases. The largest number of cases was recorded at Peshawar in the extreme north-west corner of India, as far from the sea-coast as possible. The cases numbered 73, and all but one of them occurred between June 24 and July 13, during an exceptionally hot spell of weather. The mean temperature during this time varied from 94° to 100° and the maximum from 103° to 117°, having reached 110° or over, in thirteen out of the twenty days. The largest number of cases occurred on days when there was also a high percentage of moisture in the air, namely over 60 per cent of saturation, and the next greatest prevalence when that figure was between 50 and 60 per cent. Moreover, the complete and sudden cessation of this terrible outbreak occurred on the very day after the sudden fall of 11° in the mean temperature and of 17° in the maximum daily reading to 83° and 90° F. respectively, and no further case occurred during the last eighteen days of July. A more complete example of the very close relationship between a heat-wave and a severe outbreak of heatstroke it would be difficult to imagine.

Once more, during the same heat-wave, heatstroke cases were very prevalent both

in the United Provinces of Agra and Oudh and at Calcutta in Lower Bengal. The case of the United Provinces is of special interest, as returns have been received from a number of stations over an area of several hundred miles in which the temperature conditions were very uniform. An analysis of the returns shows a marked tendency for cases to occur in widely separated places on the very same days, which were also those of specially high temperatures. For example, on June 23 the highest mean temperature of the year at Cawnpore (which is near the centre of this province) was registered, namely 101.7° , the maximum being 110.5° . On that day no less than 12 cases of heatstroke occurred, this being by far the largest number in the province on any one day during the three years' records. What is still more striking is the fact that they were spread over no less than six different stations in the province : truly a remarkable coincidence if they were of microbic origin. Here, again, the decline of the cases was sudden and coincided with a marked fall in temperature, although this happened at an earlier date than that at Peshawar on account of the rains breaking sooner in the United Provinces.

Yet again, in the same hot year a well-marked group of cases occurred in the stations in the south-east of the Punjab, from July 26 to 30, also repeatedly affecting two or more places on the same days. On the previous twelve days only 1 case had been reported in those stations in the Punjab, of which I possess returns, yet 17 cases occurred during these five days, when the mean temperature at the most affected station varied from 94° to 98° and the maximum from 103° to 109° F. This outburst also ceased immediately after a sudden fall of the mean temperature to 88° and the maximum to 94° .

In 1906 there was an outbreak in the Punjab at the end of June coinciding with a mean temperature of from 97° to 102° and a maximum of from 107° to 112° , and a number of cases occurred in the same province during July under very similar temperature conditions. The next greatest prevalence was in the United Provinces during the third week in June, when the mean temperature was from 96° to 99° and the maximum from 103° to 110° . As soon as the temperature fell rapidly to 87° mean and 91° maximum the cases ceased, except for 1 on a day when the moisture showed the very high figure of 83 per cent of saturation with a mean temperature of 88° . This case is of importance, as it is a type of the exceptional instances in which one or two cases occur for a day or two after a marked fall in the temperature conditions. Such a decline is generally brought about by a heavy fall of rain, or less commonly by a dust-storm without much actual rainfall. As a result of the rain the air becomes saturated with moisture, and it may be followed on the cessation of the rain by an extremely trying damp muggy heat, such as I have shown often coincides with heatstroke, in spite of the temperature not being extremely high. In this way the occurrence of these lagging cases is readily explained on physiological grounds, so that they lend no support to the microbic theory of the causation of heatstroke.

As the above instances include all those in my returns for the three years dealt with in which any considerable number of cases occurred at about the same time in any one place or province of India, it may confidently be asserted that there is a most marked relationship between heat-waves and the outbreak of heatstroke throughout this vast country, the degree of moisture in the air being also taken into account, and all these outbreaks are, therefore, readily explainable on the hypothesis that heat is the exciting

cause of the disease. The statement of Sambon and Manson that heatstroke cases occur quite capriciously and that they are independent of the temperature conditions is thus seen to be totally untrue as regards the prevalence of the disease in India. I am also informed by Professor Osler that an exactly similar relationship between heatstroke and heat-waves exists in the United States, so that it is probably true of all parts of the world.

Thus Gauss and Meyer have recorded that during the record temperature in Chicago in July 1916 with a mean monthly temperature of 78·4° F., 158 cases of heatstroke occurred with a mortality of 44·3 per cent. Lambert in New York during the occurrence of 805 cases noted a temperature of 36·5° C. (97·7° F.) with 70 per cent of saturation. Grandis in Buenos Aires met with a number of cases during a temperature of 39·8° C. (103·6° F.) with very high humidity. Cases have been reported among men working in the engine-rooms of ships at very high temperatures by Fiske, Neilson, Bruno and others. In the dry heat of the Sudan Balfour states that heatstroke is rare, but notes that Crispin found it to be more common in the moist heat of the Red Sea coast. All these records are in agreement with the conclusions I have come to from the analysis of the large number of cases in India, while Pembrey, in an examination of records of 50 Indian cases occurring between June 1909 and September 1910, arrived at very similar conclusions, and pointed out the great value of the wet-bulb reading, which is well illustrated by the figures of the following table showing the percentages of cases occurring with different wet-bulb readings in both Pembrey's and my series of cases, the latter having been worked out in this form by R. J. S. Simpson.

TABLE XLII.

Wet-Bulb Temperature	Pembrey's Cases.	Per-cent-age.	Wet-Bulb Temperature.	Rogers Cases.	Percentage.
80° F. or over	25	..	68-70° F.	5	1·4
84° F. or over	8	76	70-79° F.	128	35·4
85° F. or over	5	..	79-90° F.	230	63·1
Under 80° F.	12

The large proportion of cases with wet-bulb readings of 79° F. and over is clearly seen.

Predisposing Causes.—Although heat modified by the moisture in the air is thus seen to be the most probable exciting factor in the disease, it is doubtless greatly aided by predisposing causes in the persons of those who succumb to the excessive tax on their heat-regulating mechanism. This is well recognized by the old Indian writers—Norman Chevers, for example, enumerating no less than twenty-four conditions which predispose to heatstroke in individuals by lowering the resisting powers or inducing exhaustion of the nervous system. Of these it is generally agreed that **alcohol** is by far the most common and important. In the tables of cases sent out by me a special column was allotted for information on this point, and an analysis of the data supplied has furnished the following results. In only 98 cases was the information available. Of these 45 were stated to be temperate, including 6 total abstainers; 25 were moderate drinkers, while the remaining 22, or nearly one-fourth of the total number, were decidedly alcoholic. Moreover, no less than one-third of the cases of heatstroke in alcoholic subjects proved fatal, or about double the proportion of the whole series. It appears, then, that alcohol both predisposes

markedly to the heatstroke and greatly increases the gravity of the cases. Pembrey notes that alcohol upsets the heat-regulating mechanism so that great heat causes an alcoholic's temperature to ascend rapidly, and records that of 7 cases in drinkers 4 were fatal, in 7 moderate drinkers 2 and of 7 abstainers only 1 died. He also mentions debility and unsuitable clothing and equipment in soldiers as predisposing causes. Hillel in the German Army in 1913 reported that 83·6 per cent of those prostrated by heat were out of condition through alcohol, obesity, sedentary occupations or chronic heart and lung diseases, extensive adhesions of the lungs being found post mortem in 36 per cent of fatal cases. Gauss and Meyer also found a majority of their cases gave a history of alcoholism.

Any debilitating illness may act as a predisposing cause, as is shown by the not uncommon occurrence of attacks in patients already in hospital for some other affection, as in Longmore's cases.

Sex and Age.—The returns being from the army give no information as to the prevalence of the disease in the different sexes. In the Calcutta European Hospital, however, for the last three years 14 cases have been admitted, all among males. This is partly due to a marked excess of male immigrants, and to the occurrence of most of the cases among sailors.

The age of nearly 90 per cent of the army cases was between 21 and 30 years, owing to the great preponderance of men of this decade in the regiments. The largest proportion of cases took place during the first year of service in India, but nearly as many occurred in each of the next two years in the country. In Calcutta, however, 6 out of 13 cases were in men of over forty years of age, which gives a truer idea of the age incidence of heatstroke than the army returns. Chevers stated that although it is true that most of the cases occur in young unseasoned men, yet this is largely due to their want of prudence, and long residence in the tropics does not lessen the predisposition to the disease. It is well known that middle-aged, rather corpulent and often alcoholic non-commissioned officers of the army are very prone to suffer from heatstroke. Gauss and Meyer found 79·8 per cent of their patients to be in the third, fourth and fifth decades of life. Pembrey records 2 deaths among 27 patients aged from 20 to 25, but 5 out of 10 aged from 39 to 41 years.

PROPHYLAXIS OF HEATSTROKE

The importance of the preceding lengthy discussion upon the nature of the exciting agent of heatstroke becomes evident when the prophylaxis of the disease comes to be considered. If it is due to an undiscovered microbe, regarding whose life-history we are totally ignorant, we must clearly await further enlightenment before we can lay down any rules for the anticipation and prevention of this formidable disease. If, on the other hand, the evidence I have adduced is considered to go far towards proving that definite climatic conditions, namely, a high temperature with a certain degree of moisture in the air, are the exciting cause, and that cases ordinarily only occur during such conditions, then it at once becomes possible to foresee an outbreak and take special measures to ensure the earliest possible detection and adequate treatment of the cases; this will certainly greatly lower

the mortality, for the recovery rate is precisely in proportion to the rapidity with which they are treated after serious symptoms have set in.

As in all stations where British regiments are stationed, as well as in all civil stations with an appreciable European population in India, meteorological data are regularly kept, it would be easy to arrange for those in charge of the instruments to give warning to the necessary authorities when "heatstroke" weather conditions are reached. In Calcutta and other tropical ports, where the great majority of the patients are European sailors, the Port Health Authority should be warned, and previously prepared printed instructions should be issued to the captains of all vessels in the port. A similar warning should be sent to the commanding and medical officers of British troops.

The main points to be attended to in these directions are the following: Firstly, all men feeling seedy or out of sorts in the morning should be directed to report themselves and be kept under close observation, in order that the earliest premonitory symptoms may be detected. Secondly, sailors resting in their quarters and soldiers in their barracks should be visited at least every half-hour during the time heatstroke cases nearly always occur, namely, from noon to late in the evening. By this means the earliest signs of severe headache, rapid or gasping respiration and the dry burning heat of the skin would be detected before the temperature had reached a very high degree and stertorous breathing and coma had set in. Thirdly, instructions should be given and provisions made for the immediate treatment of the cases on the spot, for the delay caused by moving the patient to hospital before cold assusions are applied is only too frequently responsible for a fatal termination. This has been strikingly the case in Calcutta in the case of sailors attacked with heatstroke in vessels on the river or in the docks with water ready at hand (a supply of ice should be always made compulsory on ships in port during heatstroke weather). Yet a native doctor is often first sent for, and after about an hour's delay he comes and says he can do nothing, and orders the man to be sent to hospital, which means another hour's delay, and but little chance of successful treatment by the time he reaches the institution. Ships' officers and the non-commissioned officers of troops could readily be instructed to commence the cold assusions in such cases, a medical man being in the meantime sent for. I am convinced that the routine adoption of some such plan as that outlined would materially reduce the death-rate, and still more the invaliding rate and serious after-effects of heatstroke in India, as well as in other tropical climates, and until the supporters of the microbic theory can adduce a little more evidence than the unproven and largely incorrect statements they at present rely on, it will be far safer to accept the very definite relationship between high temperatures and moisture and heatstroke prevalence which I have shown to obtain throughout the very varying climatic conditions of India, and to put into operation the above simple prophylactic measures based on this knowledge. For the **prevention of sunstroke** suitable headgear is the most important measure. There has been much discussion on the proper colour of the inner lining of helmets, red or yellow to keep out the actinic rays of the sun having been advised. Puntoni in Italy tested the power of the dead tissues of the human cranium to stop the penetration of various rays and found it diathermal to both the red-yellow and the violet-ultraviolet, but absorbed the red and green-blue rays. He also experimented with albino rats, which are very susceptible to sunstroke, and found that the violet-ultraviolet rays caused death from sunstroke in

25 to 30 minutes, but that the red-yellow rays so killed in a longer time with different symptoms. He therefore advises green glasses and green clothing, covered with white on account of its reflecting properties. Experiments in India with different coloured linings to helmets proved that they made no difference to the inside temperature, but good ventilation was found to be most important. Duncan recommended tinted glasses as preferable to coloured ones, loose clothing and a spinal pad.

Mild Forms of Fever due to Heat.—All the older writers on fevers in India ascribed to the effects of heat, in addition to true heatstroke, certain milder forms, which they called "ephemeral" and "ardent" fever. They probably included under these terms the seven-day and three-day fevers described as unclassified specific short fevers on p. 308. The question remains : Are there any other short mild fevers, without the actual hyperpyrexia and loss of consciousness of true heatstroke, which are nevertheless produced in the same way by failure of the heat-regulating mechanism of the body when exposed for long to exceptionally high, and often also moist, temperatures ? Among my two years' complete fever records of the European Hospital, Calcutta, there are a very few cases occurring during heatstroke weather which could not be classed as either malarial or seven-day fever. In some of them there was a history of preceding exposure to the sun or working in very hot places, while headache was a prominent feature. Moreover, the temperature curves showed a low continued or intermittent fever, closely resembling that which is shown in Chart 80 as following true heatstroke. For these reasons I am inclined to consider them as mild forms of heat fever. It is noteworthy that they only numbered about ten cases in the two years ; thus they form a very minute proportion of fevers in Calcutta.

CLINICAL DESCRIPTION OF HEATSTROKE

Premonitory Symptoms.—The warning symptoms which sometimes precede the actual loss of consciousness are very important, as the prognosis of the case is good in proportion to the rapidity with which the condition is detected and adequately treated. The tendency of heatstroke to supervene on other debilitating illnesses, sometimes in people already in hospital, has already been mentioned. In 5 of Longmore's 16 cases there had been previous fever, but in the other 11 the attack was a sudden one. Of my 14 Calcutta cases in 1 there had been fever for seven days before the attack ; in 3 the patient had been feeling seedy for from three to seven days ; in 1 he had felt unwell the evening before, and in 4 had been feeling out of sorts or slightly feverish during the morning only of the attack. The last are the most important, as in "heatstroke weather"—as Chevers terms the very hot oppressive days on which alone heatstroke cases occur in Calcutta—the careful watching of any persons who feel out of sorts would enable many of these cases to be detected on the first onset of serious symptoms, when treatment will probably be always attended with a successful result. Headache is another fairly common premonitory symptom, which was noted in three of my cases, and is mentioned by other writers, together with listlessness, drowsiness and, as Longmore first pointed out, *a desire to micturate freely*, which he suggests may be "a metastasis of function to the urinary apparatus on

the secretion of the skin being diminished." This warning sign is especially noteworthy, as it points to an actually increased secretion of urine (Longmore having drawn off much urine from the bladder of a recovering case) such as would naturally coincide with the sudden cessation of active sweating, which is such a marked feature of heatstroke cases with their hot, burning and absolutely dry skins.

The Onset of the Attack.—The essential symptom of the developed attack is hyperpyrexia with the unconsciousness which always accompanies great elevations of the body temperature. The attack may be immediately preceded by faintness, sense of great oppression, sudden pain in the head or chest and vertigo. On examination during the fully developed attack the most noteworthy feature is the intense heat of the skin and its dryness, with no trace of perspiration, even in the sweat-producing damp temperature of Calcutta heatstroke weather. In one Calcutta case there was a definite history of the hyperpyrexia and unconsciousness shortly following the cessation of free perspiration. This points to a cessation of the functions of the skin as an essential factor in the production of the hyperpyrexia, which in turn will by itself fully explain the other symptoms met with without the assumption of any microbe-produced toxin.

The Pulse is rapid, feeble in force, and may be irregular or excited in its action.

The Respirations are also increased in frequency, usually to a very marked extent, and of a gasping or often a stertorous character. In bad cases marked cyanosis of the face and extremities ensues, and is of very bad prognostic significance. On auscultating the lungs extensive moist sounds are heard, indicating a rapid oedema of the organ and secretion of fluid into the bronchial tubes, which appears to be an important element in producing a fatal termination. This may be so marked and rapid that it appears to me to be largely of the nature of a vicarious secretion of fluid in the place of the suppressed perspiration, and thus a parallel phenomenon with the increased secretion of urine.

Bowels.—Motions are frequently passed involuntarily in bed, and this may occur in cases which eventually recover. This appears to be due to a loss of control of the higher centres over those in the lumbar cord with the onset of unconsciousness.

Sickness also occurs either in an early stage or during more or less complete recovery of consciousness.

The Pupils are usually contracted, but in two Calcutta cases, which recovered, they were dilated.

Rigidity of Muscles or Convulsions not uncommonly occur, and when marked indicate a bad prognosis. I have, however, seen a condition of tetany ensue with a fall in the temperature in a recovering case.

The Hyperpyrexia and Unconsciousness are the most constant and important symptoms.

The following table shows the highest temperature reached in 49 cases reported by Pembrey and 12 of my Calcutta cases, together with the mortality in different groups.

TABLE XLIII.

Maximum Temperature.	Cases.	Deaths.	Percentage Mortality.
Below 107° F. . . .	24	2	8·3
107-108° F. . . .	14	4	29·2
108-109° F. . . .	10	3	
109-110° F. . . .	8	4	69·2
110-111° F. . . .	5	5	
Total	61	18	29·5

The most striking thing about these data is the number of recoveries from hyperpyrexia up to 109° and 108° F. If these sudden excessive temperatures are due to the toxin of a microbe it must be of an extremely virulent nature. Yet it must suddenly produce these high temperatures, usually with only a few hours' previous slight indisposition, or even none at all, and the condition must as rapidly pass away, when the cases come early under observation (see below), as a result of the simple process of abstracting heat from the body by cold douching. Are we to believe that the toxins circulating in the blood are immediately destroyed by the external application of cold? Is there any other example known of such serious toxic symptoms being thus easily and rapidly relieved? This difficulty alone seems to me to be fatal to the microbial theory of the causation of heatstroke.

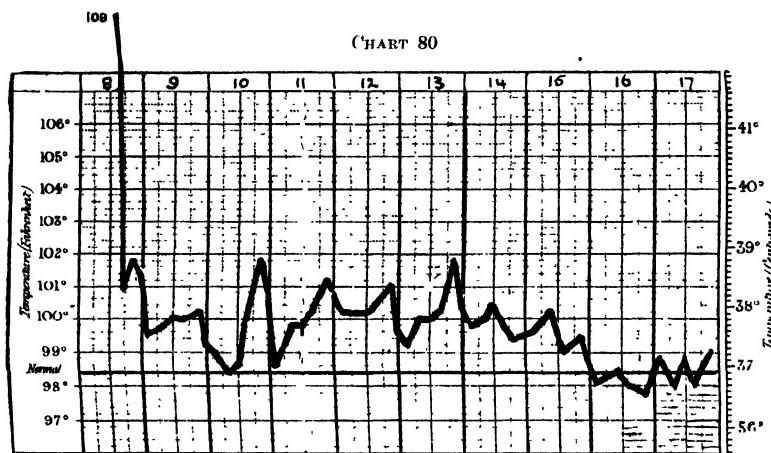
Time of Treatment in Relationship to Prognosis.—There is no exact relationship between the actual degree of hyperpyrexia at the time of admission and the mortality, although the death-rate naturally increases with the height to which the temperature rises. There is, however, a very definite one between the length of time the serious symptoms of unconsciousness have persisted before adequate treatment is adopted and the death-rate. Thus in my Calcutta cases the average duration of unconsciousness before admission in the fatal cases was $3\frac{1}{2}$ hours, although the longest period was but $4\frac{1}{2}$ hours, but in those which recovered it averaged but $1\frac{1}{3}$ hours. The importance of this fact in the prophylaxis of the disease will be evident.

After Fever.—After the temperature has been brought down by cold applications a low form of fever, shown in Chart 80, is commonly seen, although in some cases it may be slight as in Chart 81. This after fever may well be explained by the heat-regulating mechanism requiring some few days to recover completely from the very severe derangement it has suffered from; this I at one time thought might be evidence of malaria on which hyperpyrexia had ensued, but in 8 of the Calcutta series I examined the blood for malarial parasites with a negative result in all. Moreover, as they did not occur in the malarial season, that disease can be excluded as a common factor in their production.

Mortality.—This varies somewhat with the degree of severity of the cases included. Thus I find that in the British Army in India from 1904 to 1909 among 1778 cases (including those dying before admission to hospital, which do not appear to have been counted in working out the admission- and death-rates per mille in the reports of the Sanitary Commissioner with the Government of India) there were 265 deaths, or 14·9 per

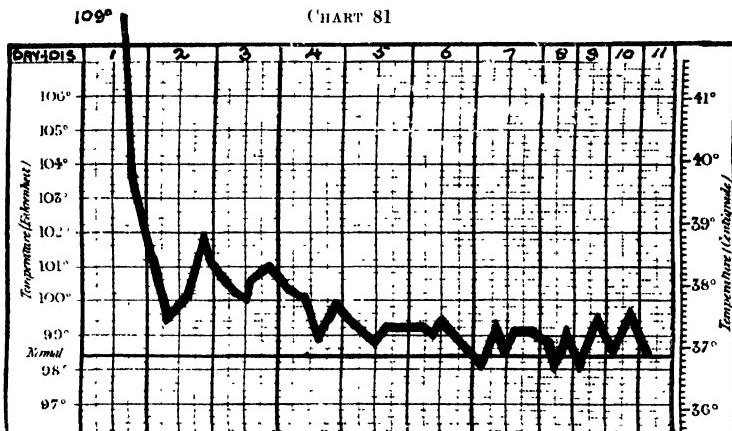
FEVERS IN THE TROPICS

cent. Many slight cases are doubtless included in these records, for the death-rate in the 61 cases reported by Pembrey and by the author was 29.5 per cent, as already mentioned, while in Chicago during a heat-wave it was no less than 44.3 per cent in 158 cases.



Heatstroke, showing hyperpyrexia followed by low secondary fever.

Sequelae.—A patient who has once suffered from heatstroke or sunstroke may be subsequently less able to stand their effects and to suffer from severe headaches on slight



Heatstroke with recovery from a temperature of 109° F.

exposure, necessitating his leaving the tropics. Insanity : Hiller met with 9.7 per cent of cases of mental disorder, usually of a neurasthenic type ; after heatstroke in the German Army while in Algeria Davera met with 11 cases of suicide in 200 cases.

Pathological Changes are somewhat variable in fatal cases. Gauss and Meyer in Chicago met with oedema of the cerebral membranes and of the lungs ; cloudy swelling of the myocardium, liver and kidneys ; fatty changes in the liver and petechial haemorrhages in the brain, viscera and skin.

TREATMENT OF HEATSTROKE

In Calcutta the absolute relationship between excessively hot weather and the occurrence of heatstroke cases is so well known that at such times special arrangements are made for the reception and immediate treatment of the patients. There are two points of primary importance in dealing with them : first, measures to lower the body temperature ; second, but not less important, those for stimulating the flagging circulatory and respiratory systems. The two can be combined in the simple method of cold affusions, by which is meant not merely placing the patient in a cold bath, but at the same time pouring cold water over the head and chest, which serves both to cool the body and to stimulate the cardiac and the respiratory centres. Instead of placing the patient in a cold bath he can be put on a stretcher with the head end raised, wrapped in a sheet and packed with ice, while cold water is poured on the head and chest as recommended by Chandler of New York, who also reports good results from the use of artificial respiration for half an hour or more when the breathing is failing. As soon as the temperature in the rectum has fallen to about 103° or 104° the cold applications should be discontinued, the patient dried and put to bed with warm bottles to lessen shock, and carefully watched. If the temperature continues to fall, and especially if sweating returns, a favourable result may be expected. If, however, the temperature again runs up rapidly the cold affusions must be repeated, but the prognosis is then more grave. Cold water enemata may also be of value, the water being cooled down to a low point with ice and given as soon as possible so as to cool down the blood in the large splanchnic area and through it that of the whole of the body.

I arranged to try in Calcutta venesection followed by intravenous injection of one pint normal salt solution at a temperature of about 60° F., to be given through the internal saphenous vein at the ankle so as to be mixed with the blood of the portal system before reaching the heart, and estimate that the whole of the blood in the body could be reduced several degrees in temperature within about five to ten minutes by such a procedure. As transfusions through the median basilic vein are often given in cholera cases at room temperature of between 70° and 80° F. when the rectal temperature is above normal, it should be quite safe to run a solution into the saphenous vein at 60° F. The solutions were kept ready at the European Hospital during hot weather at the required temperature in thermos flasks in the cool room of the kitchen, but in the only case which occurred the patient regained consciousness under cold douching just as I was about to try the treatment. In the less extreme cases probably cold water enemata and douching generally suffice, but in desperate cases with persistent temperature I think that venesection followed by a cold saline injection through the saphenous vein would be worth trying, especially as the removal of some blood would tend to lessen the meningeal congestion, which is sometimes found post mortem after fatal heatstroke. If cooling down the blood

circulating through the brain is the best method of treatment, as appears to be the case, the above is the most rapid way of accomplishing it.

Drug treatment consists in cardiac tonics hypodermically, of which digitalis is preferable to strychnine on account of the tendency to convulsions in the disease, but I have seen apparently good results follow the use even of strychnine, although some writers say it should never be given in heatstroke. Ether may also be injected over the heart in bad cases. Quinine is usually advised to be given hypodermically if malaria is suspected. I have seen it followed by return of consciousness in a bad case with continued insensibility after a marked reduction of the temperature, but without malarial parasites in the blood, and think it should always be used, guarded by cardiac tonics, as it is likely to help in restoring the control of the heat-regulating mechanism. Probably it would be more effective if cautiously administered intravenously on account of the slow absorption of hypodermic injections of the drug (see p. 267). Creosote, 10 to 15 minims, rubbed into the axilla produces profuse perspiration in a short time in fevers, and I reported several years ago its successful use in cutting short paroxysms of malaria. It would be well worthy of trial in heatstroke in order to produce diaphoresis.

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XVII. INCIDENCE OF VARIOUS SPECIFIC FEVERS IN THE TROPICAL EAST—CEREBRO-SPINAL FEVER—INFLUENZA— EXANTHEMATOUS DISEASES

CEREBRO-SPINAL FEVER IN INDIA

It is only within recent years that cerebro-spinal fever has attracted much attention in India, although its existence in the country has long been known. Norman Chevers in 1886 refers to 3 cases seen in Calcutta, but he had never known it occur in an epidemic form. Vandyke Carter records 4 cases seen in Bombay when he was working at famine fever in 1878, and describes fully the lesions found post mortem. He met with another sporadic case in 1885. According to C. J. Robertson-Milne, I.M.S. (to whose report on two years' special duty investigating the disease in India I am indebted for some references), the disease was first accurately described in this country in a report by H. P. Dimmock, I.M.S. (now Principal of the Grant Medical College, Bombay), in an unpublished report on an outbreak among the convicts of the Shikarpur jail in the cold season of 1883-84, while working on the Indus river bridge at Sukkur, 38 cases with 27 deaths occurring, a mortality of 71 per cent. In 1886 an outbreak in the Nara jail in Sind was described, and in 1889, 14 cases with 11 deaths were reported by Morehead in the Hazariabagh jail in Chota Nagpur. In 1884-85 the disease was prevalent in Calcutta and neighbouring districts, and the Alipore jail (in a suburb of Calcutta) was attacked in the latter year, the infection proving to be very persistent, as cases continued to occur there in no less than nine of the next ten years and again in 1898, since which time it appears to have abated. The Rungpore jail in North-Eastern Bengal was attacked in 1891, that of Raipur in the Central Provinces in 1899, while in the following seven years the disease has been reported from a number of jails in every important province of India, as will be seen from the references given at the end of this section.

The most important, because most closely studied, of these jail outbreaks is the series of cases occurring in the Bhagulpur (Bihar) central jail from 1897 to 1904, reported on by W. J. Buchanan, C. S. Stevens and E. A. R. Newman, all of the I.M.S., 100 cases with 70 deaths having been recorded during this period. The diplococcus of Weichselbaum was first isolated and identified by F. P. Drury, I.M.S., from one of these cases in 1899, and again by the writer in 1900 and on subsequent occasions, thus proving the identity of the disease with that of temperate climates. A noteworthy feature of the Bhagulpur series, which has been pointed out by Stevens and confirmed by Newman, is the special incidence of the disease among those convicts who were employed in dusty forms of labour,

which, together with the manner in which the infection has clung to the jail year after year, has led these writers to suggest that the organism of the disease lives for a long time in dust, through which the infection is carried, and they quote Germano's experiments on the long survival of the organism of the disease in dry dust as supporting their contention. All other bacteriologists, however, are of the opinion that the diplococcus of Weichselbaum has extremely little resisting power. My own experience with the coccus isolated from cases in Bhagulpur and Calcutta agrees with the latter opinion. Moreover, Milne has repeated Germano's experiment with organisms derived from Indian cases of cerebro-spinal fever and been quite unable to confirm them, for he only once succeeded in recovering the organism as late as the eleventh day, after mixing it with dust, his other experiments having given entirely negative results. Moreover, most of the Bhagulpur cases of the disease occurred in the hottest and driest months, when the conditions are most unfavourable to the survival of the organism outside the body. Further, many of the cases occurred in persons recently admitted to the jail, while the disease has been found to occur in the surrounding district. European workers have also recovered the organism from the noses and throats of healthy people, in much the same way as in the case of the closely allied pneumococcus. The real relationship of dusty occupations to the incidence of cerebro-spinal fever in jails may therefore be due to its irritant effect serving as a predisposing rather than an exciting cause.

In addition to the jail outbreaks, the disease has repeatedly appeared among coolies in the Calcutta emigration depots, and has been especially studied there by E. H. Brown, I.M.S., and myself, the presence of the diplococcus of Weichselbaum having been repeatedly verified both by lumbar puncture and post mortem by me, as well as in other sporadic cases occurring during the last six years in Calcutta hospitals. These coolies come chiefly from Bengal, the United Provinces and the Central Provinces, and they probably bring the infection with them, in some instances, as shown by the attacks occasionally occurring very soon after their arrival in Calcutta.

The clinical features of the disease among these coolies have been studied by E. H. Brown, who divides them into four types. Firstly, fulminant cases commencing suddenly with pain in the head and back of neck, always without any retraction, temperature 103° or more without a rigor, frequent vomiting, and death in five to eighteen hours, only congestion of the cerebral membranes being found post mortem. They may be mistaken for heatstroke or plague, and comprised 7 out of 53 cases. Secondly, acute cases, 25 in number, showing the typical characters of the disease, and ending fatally in 80 per cent in two to six days. These commenced as in the first class, but with retraction of the head and Kernig's sign well marked, decubitus being lateral with legs drawn up, the case ending with coma. Thirdly, 15 cases of a subacute or chronic type, with more gradual onset, irregular remittent temperature, retraction of the head and drowsiness, and frequently petechial or macular spots. Great emaciation ensues; as many as 60 per cent of the entire number eventually died. Lastly, in 6 cases an atypical course was seen, commencing suddenly with high fever, but ending in rapid recovery as if the disease had aborted. This occurred mostly in young persons.

Diagnosis.—In typical instances of cerebro-spinal meningitis there can be little diffi-

culty in recognizing the cases clinically. In doubtful ones the presence of leucocytosis of the polynuclear type (over 90 per cent) often is of value. In one case I examined the blood to decide if the disease was typhoid or not. Of still greater value is lumbar puncture, which enables the diplococcus of Weichselbaum to be found microscopically in large numbers in the polynuclear leucocytes, and cultures to be made on glycerine agar, at least 1 c.c. of fluid being added to each of several tubes of glycerine agar, when a few colonies only are usually obtained. By this measure as much as 10 c.c. or more of fluid is often removed ; this relieves the retraction of the head for a time. Moreover, repetition of the process certainly appears to have a good effect, and may save a few patients. A strong needle, about three inches in length, is required for the purpose, and it should be passed inwards and slightly upwards and towards the middle line through the second or third lumbar space. The fluid will readily escape by its own pressure, and no suction should be applied.

Prophylaxis will remain uncertain until the mode of infection is clearly understood.

INFLUENZA

All the older great epidemics of influenza in Europe spread from the East through Russia, but the first in which the course of the disease in Asia is given by Lichtenstern, in *Nothnagel's Encyclopedia of Medicine*, is that of 1830-33, which originated in China, and spread by the East Indies and India to Russia, while that of 1836-37 affected Java and Farther India. It is not, however, until we come to the last great pandemic beginning in 1889-90 that we have any accurate records of influenza in the East. This originated in the interior of Turkestan in May 1889, and spread once more through Russia to Europe, across to America, and back to the East, to reach Hongkong by February 1890. From that great port it travelled by ship to China, Farther India, and the East Indies, to reach Bombay in India proper at the end of February, the United Provinces and Calcutta in the beginning of March, and Burma early in April : thus encircling the globe within a single year.

The disease continued to be widespread in India during the next two years and was very prevalent in the early months of 1892, when it caused a marked increase in the mortality ascribed to "fever" in Assam during March and April, which are usually the most healthy months of the year. In order to ascertain the seasonal prevalence and characters of the disease in India I have analysed all the cases which were admitted to the European General Hospital, Calcutta, for the year 1892, with the following results.

Seasonal Prevalence in Calcutta in 1892.—Table XLIV. shows the monthly prevalence of influenza in Calcutta in 1892.

Thus, a few cases occurred in January, near the end of the month, while over half of the annual total were admitted during February, and one-third more in March. The cases began to decrease after the middle of March and only one patient was admitted during April who had contracted the disease during the previous month. From April to August no new infections arose, but in September, and to a less extent in October, a

number of fever cases were returned as influenza. On examining the records closely, however, it was ascertained that all these autumnal cases had been diagnosed by one of

TABLE XLIV.—MONTHLY INCIDENCE OF INFLUENZA IN CALCUTTA

Cases	January.	February.	March.	April.	May.	June.	July.	August.	September.	October.	November.	December.	Total.
	6	54	33	1	0	0	0	0	?	?	0	0	94

the three medical officers of the hospital, no cases having been met with by the other two. Further, the lung and throat symptoms, which had been nearly constantly recorded in the early part of the year, were conspicuously absent in these later cases, while their temperature charts were in many of them typical of either malarial or seven-day fever, and did not correspond with those of the influenza cases seen in February and March. It is therefore extremely doubtful if any of these later returned cases were really influenza, while the great majority of them were certainly not that fever. For this reason ? has been entered in the table against the months of September and October.

In 1906 I also met with a few cases of influenza which all occurred in February, March and early April, as in the 1892 outbreak. This seasonal distribution is in agreement with the much greater prevalence of the disease during the winter months in Europe; and the complete disappearance of influenza in the hot months of the year in Calcutta is noteworthy and important, for it is not until the hot weather is well established that the seven-day fever appears, only to disappear again towards the end of the rainy season in October or November, when the air temperature cools down considerably. This divergence of the seasonal incidence of these two diseases simplifies their differentiation greatly, for in its mode of onset with pains and aches, and in its spread, seven-day fever so closely resembles influenza that I was led in my preliminary description of the former disease to call it provisionally "a peculiar influenza-like fever."

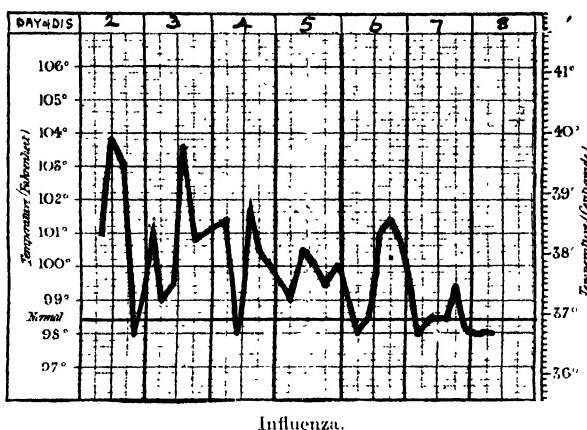
BRIEF CLINICAL DESCRIPTION

The records of the influenza cases in Calcutta in 1892 show no important differences in the disease from the type seen in Europe at the same period. Only the principal characteristics, therefore, require mention here, especially those in which it differs from other common fevers of the East.

The sudden onset, often with chilliness or actual rigor, with severe pains in the back or all over the body, was a well-marked feature. More significant still was the great frequency of respiratory and throat complications, both of which are but very rarely met with in malaria and seven-day fever. Thus, in over one-third of the cases rales or rhonchi were heard in the lungs, and in 10 per cent more the breathing was recorded as being harsh. Cough, often of a very persistent nature, was almost always present, and frequently very troublesome. Pneumonia occurred in 3 of the 94 cases, proving fatal in one of them,

while meningitis produced death in a second, and exhaustion in a third case. Another very prominent symptom was congestion or inflammation of the throat, which was recorded in about half the cases, although in a good many the records were deficient. In fact, in

CHART 82.



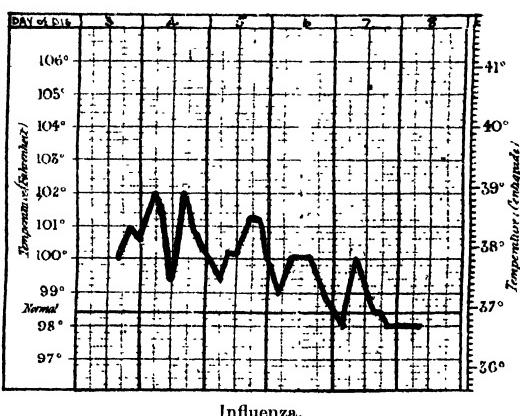
intermittent type, rising in the afternoon and falling at night as shown in Charts 82 to 84. In no case was anything approaching the continued saddle-back type chart of seven-day fever seen in influenza. In more severe cases irregular remittent fever of long duration may occur, especially if complicated by pneumonia, as in the fatal case shown in Chart 85. The markedly remittent character of this curve is partly due to the adoption of the terribly depressant treatment by antipyrin and antifebrin of the early 'nineties, which is now, happily, rarely used in the tropics.

less than 10 per cent were both the lungs and the throat recorded as being healthy; these two symptoms, being many times more common in influenza than in any other fever of the tropics it is likely to be confused with, are of the greatest diagnostic significance. Coryza was also not infrequently noted.

The Temperature Curve.—

The course and duration of the fever varied greatly, more particularly when complications were present. It was most frequently of a low remittent or

('HART 83



day fever, being commonly shorter, but also liable to run on much longer in the severe and complicated cases.

Blood Changes.—The haemoglobin and red corpuscles are nearly always normal. Leucocytosis does not occur except when influenza is complicated by croupous pneumonia. In the more frequent catarrhal pneumonia only a slight increase or else none at all is found. As both typhoid and seven-day fever also show an absence of leucocytosis these blood changes have very little diagnostic value. According to nearly all workers the influenza bacillus is absent from the peripheral blood ; so that cultures from the blood afford no positive diagnostic help.

Differential Diagnosis of Influenza.—

The occurrence of the disease exclusively in the colder months; the frequency of cough and of lung and throat complications; and the irregular low remittent or daily intermittent temperature curve, as opposed to the characteristic charts of malaria and seven-day fever, will usually suffice for the differential diagnosis of influenza.

CHART 84

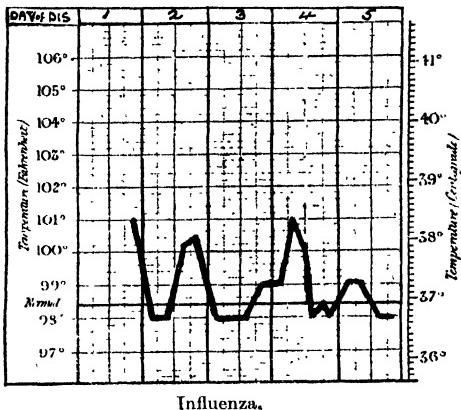
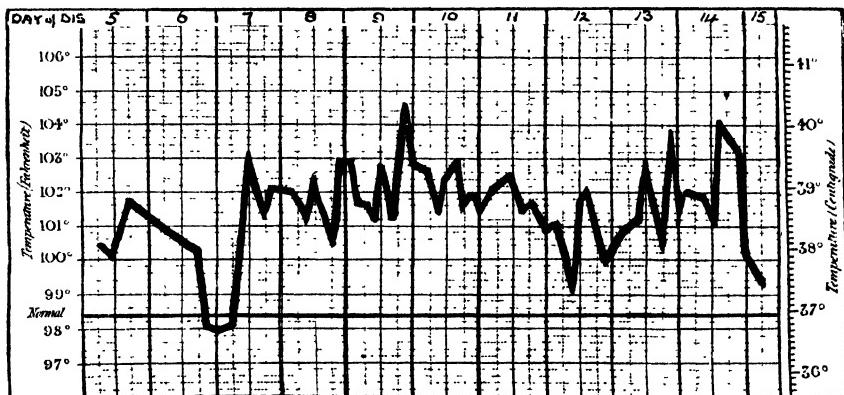


CHART 85



Influenza complicated by Pneumonia, terminating fatally.

Treatment.—This does not differ from that of the disease in temperate climates, except that severe inflammatory lung complications are more rarely met with.

Rheumatic Fever.—Tropical countries differ in a remarkable way from temperate in the almost complete absence of rheumatic fever. Rheumatic fever does occur in hill stations in the Himalayas with European temperatures, but is scarcely ever seen in the hot plains; as a result of the absence of both rheumatic fever and scarlet fever heart diseases differ widely in their incidence. Other affections due mainly to syphilitic atheroma are very common, and organic lesions of the mitral valves proportionately rarer.

PREVALENCE OF THE EXANTHEMATOUS DISEASES IN THE EAST

TABLE XLV.—MONTHLY AND QUARTERLY PREVALENCE OF EXANTHEMATA
IN EUROPEANS IN CALCUTTA

	January.	February.	March.	April.	May.	June.	July.	August.	September.	October.	November.	December.	Total.
Scarlet fever	0
Measles . .	25	24	49	31	12	5	2	7	4	4	13	19	195
Quarterly . .	98			48			13				36		
German measles	
Mumps . .	5	7	11	4	5	3	2	6	5	
Quarterly . .	23			12			13			0			48
Whooping-cough . .	2	3	..	3	2	3	4	9	11	6	7	4	
Quarterly . .	5			8			24			17			54
Chicken-pox . .	6	17	6	1	5	..	2	..	5	1	21		
Quarterly . .	29			6			2			27			64
Diphtheria . .	3	..	2	1	1	1	3	3	
Quarterly . .	5			3			..			6			14

The total and seasonal prevalence of the various acute exanthematous diseases in the tropical East differ greatly from those of temperate parts of Europe and America. A brief account of the main variations may therefore be of use to medical men practising in those parts. Table XLV., showing the monthly distribution of this group of diseases in the European Hospital, Calcutta, for the last three years, for which I am indebted to Assistant-Surgeon A. A. E. Baptist, will serve to illustrate the main points.

Scarlet Fever in India.—Unlike measles and the other exanthematous diseases of temperate climates, scarlet fever is very rarely met with in India, its very occurrence in the country having been called in question as late as 1871, when a controversy on the subject arose in the columns of the *Indian Medical Gazette* over a case reported to have been seen in Simla, and several very definite instances of the disease being imported into India by troopships, and spreading to a limited extent, were recorded. Thus 13 cases were reported by Gibson with typical rash on the second day, strawberry tongue, inflammation

of the tonsils, pharynx and salivary gland, albuminuria and dropsy in 6 cases, and discharges from the nose and ears causing deafness in one instance, all occurring among the children of a British regiment. Again, the disease broke out at both Sialkote and Jullundur in the Punjab among the children who came to India by the same trooper, on whose voyage several cases of scarlatina had occurred, the attacks being very similar to those just mentioned, while several fatal cases occurred. Since that time many similar importations of the disease have taken place, some of which appear to have been due to infection from clothes, etc., through the post, from infected houses in England ; but it only gives rise to very limited outbreaks and rapidly dies out.

On the other hand, a careful inquiry from the most experienced medical men in Calcutta in 1871, including Norman Chevers, Fayrer, Ewart and Edmonstone Charles, revealed a general agreement that scarlatina had not been seen in Calcutta, although cases of the dengue-like red fever described by E. Goodeve had sometimes been mistaken for it. Since that date a few cases have been returned annually among British troops, isolated ones have been reported in Calcutta by R. D. Murray, Kailas Chunder Bose, A. Caddy and J. Nield Cook, a micrococcus having been isolated by the last two observers, which is said to have produced the Hendon disease in calves inoculated with it. A very limited outbreak in 1902 was reported from Ranchi, in Chota Nagpur, at a height of 2000 feet, by R. H. Maddox, I.M.S. No cases were admitted to the Calcutta European Hospital in the last three years. The disease appears to be equally rare in Southern China and other tropical parts.

It is clear, then, that scarlatina does occur in India as an imported infection, but that it is usually of a mild nature, and shows no tendency to spread widely, but on the contrary rapidly dies out, especially in the hotter parts of India. There is no evidence that it ever becomes an indigenous disease ; it rarely if ever attacks natives of the country.

Measles.—In marked contrast to scarlet fever, measles is common all over the tropical East, and especially in India. It is the most frequently-met-with exanthem in Calcutta, 195 cases having been seen in the European Hospital in the three years 1904–6. The seasonal distribution is noteworthy : five-sixths of the cases occurred in the six colder months from November to April, while they were much fewer in the hot and rainy seasons. The British naval reports show 41 cases of measles in the East Indian squadron, and 16 in the China station, in the ten years from 1895 to 1905.

German Measles.—Only one case of German measles occurs in the Calcutta Hospital series, but the disease was fairly prevalent in Calcutta in the cold season of 1906–7 ; it was usually so mild as to be treated at home. It appears to be still more common on the China stations, where 58 cases occurred in ten years in the naval squadron.

Mumps.—Another common disease in India is mumps, which attacks natives as well as Europeans, being far from rare in the native army in the cold season. In the Calcutta Hospital most cases were seen in the early part of the year, and fewest in the autumn months. The disease has also occurred in China ports in some years in the navy. According to Clemow it is probably rare in the East India Islands.

Whooping-cough.—Whooping-cough also occurs throughout the year in Calcutta, being most frequent in the rainy season, in which respect it differs from the rest of this class of diseases. I have not found it recorded in the naval reports for the China station, but Clemow states that it is not rare in that country.

Chicken-pox.—Another common disease throughout the tropical East is chicken-pox, and here there is often great difficulty in distinguishing its severer forms from mild and modified small-pox. The blood changes in these two conditions are worthy of closer study from this point of view than they have yet received. Chicken-pox is also most prevalent in the cold season, 44 out of 64 Calcutta cases having been admitted in the three coldest months of the year from December to February, while very few occurred in the hot and rainy months.

Small-pox.—Small-pox is endemic in the tropical East, where it has been known for many centuries. In India the majority of elderly natives still show pitting of the face produced by the disease, although this is much less common among the young adults and children, thanks to vaccination. Inoculation marks can be found on the forearms of many of the older Mohammedans, especially in Eastern Bengal. Small-pox is never absent for more than a few months at a time from Calcutta, where the maximum incidence is during the dry, cold and hot weather months from October to the following May, and the minimum in the remaining monsoon period, although a marked decline occurs before the rains actually set in. An interesting account of the disease in Calcutta has recently been recorded by J. C. Vaughan, I.M.S.

Diphtheria.—Diphtheria is fortunately much less common in the tropical East than in temperate parts of Europe and America. It does occur in Calcutta, and also in China, being also much more frequent in the cold season, and especially rare in the rains. It may occur in hill stations at any season. Antitoxic serum in sufficient doses has just as good an effect in India as in other places ; it should therefore be always available where likely to be required.

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THE END

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